8. ASSESSMENT OF INCREASED RISK FOR RESPIRATORY ILLNESSES IN CHILDREN FROM ENVIRONMENTAL TOBACCO SMOKE

In the preceding chapter, a review was presented of recently published studies regarding the association between respiratory illnesses in children and environmental tobacco smoke (ETS) exposure. The biological plausibility and the possible pathogenetic mechanisms involved in each group of illnesses included in the chapter were also discussed. The purpose of this chapter is to consider the weight of the evidence as a whole, to analyze in detail possible sources of systematic bias or confounding that may explain the observed associations, and to estimate the population impact of ETS-associated respiratory illnesses.

8.1. POSSIBLE ROLE OF CONFOUNDING

In the review of the available evidence indicating an association (or lack thereof) between ETS exposure and the different outcomes considered in this report, the possible role of several confounding factors was analyzed in detail (see Chapter 7). Such analysis will only be summarized here.

- Other indoor air pollutants (wood smoke, NO_2, formaldehyde, etc.) have not been found to explain the effects of ETS, but may interact with it to increase the risk of both respiratory illnesses and of decreased lung function in children.
- Many of the studies reviewed in this report and in those of the National Research Council (NRC) (1986) and the Surgeon General (U.S. DHHS, 1986) used either multivariate statistical methods of analysis or poststratification of the sample to control for the possible confounding effects of socioeconomic status. Others controlled for this effect by study design. It can be concluded that socioeconomic status does not explain the reported effects of ETS on children's health, although children belonging to some social groups may be at increased risk of suffering the effects of passive smoking (see also Section 8.3).
- The effect of parental symptoms on the association between ETS and child health has also been extensively analyzed. It can be concluded that, although parents with symptoms may be more aware of their children's symptoms than are parents without symptoms, it is unlikely that this fact by itself explains the association. In fact, objective parameters of lung function, bronchial responsiveness, and atopy,

which are not subject to such sources of bias, have been found to be altered in children exposed to ETS.

- The effects of passive smoking may be modified by several characteristics of the exposed child. Increased risk has been reported in premature infants and infants of low birthweight, infants who are not breast-fed, infants who are kept at home with smoking mothers and not sent to day-care centers, asthmatic children, and children who are active smokers.
- Maternal smoking during pregnancy has significant effects on fetal growth and development and may affect lung growth as well as the immunologic system. However, reports of important effects of paternal smoking on the child's health and studies in which ETS exposure was found to have effects that were independent of in utero exposure indicate that maternal smoking during pregnancy does not explain the relation between passive smoking and child health, but modifies the effects of ETS.

In summary, there is no single or combined confounding factors that can explain the observed respiratory effects of passive smoking in children.

8.2. MISCLASSIFICATION OF EXPOSED AND UNEXPOSED SUBJECTS

The importance of misclassification of exposed and unexposed children has not been addressed and will be analyzed in detail below.

Two possible sources of systematic bias related to subject misclassification are considered. The first is upward bias from the effect of active smoking in children; the second is downward bias due to misreporting and background exposure. Both have also been considered in the assessment of ETS and lung cancer in adults. Adjustment for background exposure will be similar to that presented in Chapter 6, except that data for increased incidence of some ETS-associated respiratory diseases show some evidence of thresholds that must also be taken into account.

8.2.1. Effect of Active Smoking in Children

The possibility needs to be considered that some children may be smokers themselves and that this may happen more often among children of smoking parents than among those of nonsmoking parents. This would bias the results upwards or against the null effect. This source of bias is only applicable to studies of older children; regular active smoking may occur but is rare before early adolescence. A study of third graders in Edinburgh, Scotland, by Strachan and

coworkers (Strachan et al., 1989, see Section 7.4.1), for example, showed that salivary cotinine levels compatible with active smoking were found in 6 of 770 children ages 6-1/2 to 7-1/2 years, suggesting only a small potential for bias. Consideration should also be given to the fact that some of the effects described in Chapter 7 (for example, the increased risks for acute respiratory illnesses [Section 7.3.1] and for cough, phlegm, and wheezing [Section 7.5.1]) have been found to be stronger in younger children (i.e., those less likely to be active smokers) than in older children. This observed reduced effect with increasing age may be in part due to an age-related increase in misclassification of exposed subjects as "unexposed" (see below), but it is clear that these specific effects of ETS *do not increase with age*, as would be expected if active smoking biased the results of studies of ETS effects in older children. It can thus be concluded that the association between respiratory health in children and ETS is not attributable to active smoking by some children. It has been suggested that active and passive smoking may interact to increase the effects of either exposure separately (Lebowitz, 1988). This interaction is biologically plausible, because it is likely that active smoking may be more harmful in children whose lungs have been previously affected by ETS (see Section 7.1).

8.2.2. Misreporting and Background Exposure

Various investigators have measured cotinine levels in body fluids in infants and children and correlated the results with parental reports of ETS exposure. Coultas and coworkers (1987) reported that 37% of children under 5 years of age whose parents were both nonsmokers had a salivary cotinine level greater than 0, compared with 32% of children ages 6 to 12 and with 35% of children ages 13 to 17. These authors did not ask parents to report possible sources of ETS exposure for their children other than their own tobacco consumption. Strachan and coworkers' study in 6-1/2- to 7-1/2-year-old children in Scotland (Strachan et al., 1989) showed that 73% of children from households with no smokers had detectable concentrations of cotinine in saliva, whereas only 1 in 365 children from households with one or more smokers had no detectable salivary cotinine. The assay used by Strachan and coworkers was 10 times more sensitive than that used by Coultas and coworkers, and this may explain the larger number of subjects with detectable levels in the former study when compared to the latter.

Greenberg and coworkers (1984) studied cotinine levels in 32 infants in North Carolina with reported exposure to tobacco smoke within the previous 24 hours and in 19 unexposed infants. All subjects were under 10 months old. Urine samples of all exposed infants contained

cotinine, whereas all unexposed infants except 2 (11%) had undetectable urine cotinine or levels below those of exposed infants with the lowest levels of urine cotinine. This same group of researchers reported results for a larger sample (433 infants at a mean age of 18 days) of the same population (Greenberg et al., 1989). They found that, of 157 infants who reportedly lived in nonsmoking households and were also not in contact with smokers the previous week, 37 infants (24%) had cotinine in their urine. They concluded that these infants had contact with tobacco smoke during the previous week and that this contact was unknown to or was not reported by their mothers.

Greenberg and coworkers (1991) followed 152 of the 433 infants originally enrolled and reassessed exposure to ETS (through maternal interviews) and urine cotinine levels when the child was 12.3 ± 0.6 months old. They found a significant increase in the prevalence of tobacco smoke absorption, indicated by excretion of cotinine, during the first year of life (from 53% at a mean age of 3 weeks to 77%). The interviews showed that this was mainly due to an increased exposure to nonhousehold sources of smoke (from 14% to 36%). The proportion of infants who reportedly had no contact with smokers but had cotinine in their urine increased from 24% at 3 weeks to 49% at 1 year of age.

These results indicate that studies that rely exclusively on parental questionnaires to ascertain ETS exposure in children may misclassify many exposed subjects as nonexposed. Moreover, the degree of misclassification may increase with the child's age.

The possible consequences of this misclassification of exposure need to be discussed in detail. Nondifferential misclassification (i.e., exposure classification that is incorrect in equal proportions of diseased and nondiseased subjects) biases the observed results towards a conclusion of no effect (Rothman, 1988; see below). The effect of differential misclassification depends on the direction in which misclassification occurs. If true ETS exposure is preferentially reported by parents of diseased subjects (i.e., there is reporting bias), an excess of disease prevalence would be found among exposed subjects when compared to unexposed subjects that is unrelated to any biological effect of ETS. The evidence available clearly indicates that this is a very unlikely explanation for the reported misclassification of ETS exposure in infants and children. In fact, reporting bias cannot explain the substantial increase in "underreporting" of exposure with age. The logical explanation is provided by the finding that exposure to nonhousehold smokers increases significantly with age and parallels the increase in the proportion of subjects who have cotinine in their urine (Greenberg et al., 1991). There is no reason to believe that exposure to smokers may occur preferentially among diseased children, and the contrary may be more

reasonable; the increased awareness of the ill effects of ETS inhalation may induce parents to limit contact between their diseased children and nonhousehold smokers. Thus, the net effect of misclassification of exposure, both nondifferential and differential, should be a systematic downward bias or bias toward observing no effect. A correction for the nondifferential misclassification bias of background exposure is made below.

8.3. ADJUSTMENT FOR BACKGROUND EXPOSURE

An important conclusion of the previous discussion is that studies based on parental questionnaires may underestimate the health risk from ETS in children due to underreporting of ETS exposure. The NRC report on passive smoking (NRC, 1986) adopted the use of cotinine measures to correct for misreporting of ETS exposure for lung cancer effects, and this approach was adapted for use in Chapter 6 of this report. It will also be employed here, with the cotinine ratios, however, based on exposure data in children rather than in adults. The method is based on several assumptions: (1) cotinine concentrations in body fluids of nonsmokers are linearly related to ETS exposure, (2) the excess risk of respiratory illness in subjects exposed to ETS is linearly related to the dose of ETS absorbed, (3) the relationship between ambient and absorbed ETS is linear, and (4) one cotinine determination may adequately represent average childhood exposure to ETS. While considerable evidence exists for assumptions 1 through 3, there is now some evidence that assumption 4 may not be entirely warranted. Coultas and coworkers (1990b) in a small study of 9 children from 10 homes with at least 1 smoker reported that there is considerable variability in cotinine levels in body fluids within individuals exposed to ETS when such levels are repeatedly measured in different days. Thus, while the method of adjustment is based on group mean body cotinine levels, which apparently reflect well household ETS levels (see below), the intraindividual variability may subject these means to some error.

Application of the algorithms proposed by the NRC requires some knowledge of Z, the ratio between the operative mean dose level in the "exposed" group, d_E, and the mean dose level in the "unexposed" group, d_N. $RR(d_E)$, the relative risk for the group identified as "exposed" compared to the group identified as "unexposed", is thus given by

$$RR(d_E) = (1+Z^*\beta d_N)/(1+\beta d_N) \qquad (8\text{-}1)$$

where β is the amount of increase per unit dose and $Z > RR(d_E) > 1$. (The "unexposed" group actually contains those with background exposure plus those truly unexposed.)

Several studies are available that could be used for the purpose of estimating Z. Jarvis and coworkers (1985) studied 569 nonsmoking schoolchildren ages 11 to 16 in Great Britain. The investigators reported that, when compared to salivary cotinine levels in children of nonsmoking parents ($N = 269$), mean levels of salivary cotinine were 3.0 times as high in children whose father smoked ($N = 96$), 4.4 times as high in children whose mother smoked, and 7.7 times as high in children whose parents were both smokers. Pattishall and coworkers (1985) reported that children from homes with smokers ($N = 20$) had 4.1 times as high mean levels of serum cotinine as children from nonsmoking families. Black children, however, in the same study had lower values of Z (2.8) than did white children. Coultas and coworkers (1987) found that, among 600 U.S. children up to age 17 years, mean salivary cotinine levels were between 1.3 and 2.6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects, and between 2.9 and 3.5 times as high among subjects exposed to two or more smokers at home as among subjects not exposed to cigarette smokers at home. Strachan and coworkers (1989) reported separate results for 6-1/2- to 7-1/2-year-old Scottish children belonging to families living in their own homes and for those belonging to families living in rented homes. In the former, geometric mean salivary cotinine was 6 times as high among subjects exposed to one cigarette smoker at home as among unexposed subjects and 16 to 17 times as high among subjects exposed to two or more smokers at home as among unexposed subjects. For children belonging to families living in rented homes, the same ratios were 3 to 5.5 times and 4 to 7 times, respectively.

While these studies show consistent relationships between mean body cotinine levels in children and home smoker occupancy, there is also a wide variability in the estimated Z ratios, ranging from 1+ to 17. These different estimates may have very important effects on the background exposure adjustment and, thus, on the calculation of adjusted relative risks for different studies (see also Chapter 6). For example, for a study in which the observed relative risk (RR) is 2.0 but for which the Z ratio is 3, equation 8-1 can be solved for βd_N, which is the estimated increase in relative risk for the group called "unexposed" but who in fact have been exposed to some recent ETS. Solving,

$$\beta d_N = 1.$$

Thus, the adjusted RR for the group identified as "unexposed" would be 2. and the adjusted RR for an "exposed" group compared to a truly unexposed group would be $1 + (3*1) = 4$, i.e., twice the observed risk. For a similar example (observed RR = 2) but with $Z = 5$, $\beta d_N = 0.3$, the RR for a

group identified as "unexposed" in this case would be 1.3, and the adjusted RR for an "exposed" to a truly unexposed group would be 2.67. Finally, if the observed RR is still 2 but Z = 17, βd_N = 0.07, RR for "unexposed" would be 1.07 and the adjusted RR for exposed children would be 2.13. These results are shown in Table 8-1.

These calculations show that when use of parental questionnaires significantly underestimates their children's exposures to other sources of ETS (other than via the parental ETS) and values of Z are lower (as found in black children by Pattishall and coworkers [1985], and in children of lower socioeconomic status by Strachan and coworkers [1989]), the "true" RR of children exposed to ETS may be considerably underestimated. But perhaps the most important conclusion that may be derived from the above analysis is that exposure to ETS from sources other than smoking parents may be high enough to constitute a significant risk for their health. This may be particularly consequential for children of lower socioeconomic levels, whose nutritional status, crowding conditions at home, and opportunity for contact with biological agents of disease make them a part of the population that is particularly susceptible to respiratory illnesses during infancy and childhood. Available data show that ETS exposure via nonhousehold members in these children, as measured by cotinine levels in body fluids, may be as much as one-third that of children exposed to one smoking parent (Z = 3). In the example presented above (observed RR = 2), the estimate of the adjusted relative risk is 4 for children of smoking parents to the truly unexposed children. However, using the same assumptions, children of *nonsmoking parents* who are exposed to ETS (at background levels found in some of the studies) would have twice as high a risk of developing the illness under study as children truly unexposed to ETS.

A cautionary note about the model is appropriate. Table 8-1 shows that, for observed RR = 2 and Z = 3, the adjusted relative risk is 4. However, as the observed RR and Z get closer together, the behavior of the model becomes erratic. This is shown in Table 8-2. In fact, the model (equation 8-1) becomes undefined if Z is less than or equal to the observed RR, and it reaches some stability only as Z becomes at least 30% to 50% greater than RR.

Fortunately, the estimates of Z presented above are appreciably greater than the observed relative risk estimates seen in Chapter 7, and in the observed range of both RR and Z, the model yields relatively stable estimates of the adjusted RR. Furthermore, as discussed in Chapter 6, the values of RR and Z are expected to be correlated for each study, i.e., the greater the Z ratio between exposed and unexposed groups in each study, the greater should be the observed RR and the less the effect of the (equation 8-1) adjustment.

If the above model is correct, then exposure of children to ETS other than at home (parental smoking) may be an important risk factor for respiratory illness in childhood. On the other hand, it is also possible that for at least some respiratory illnesses, outside exposure to ETS has relatively little effect, either because outside exposures in younger children tend to be less than those of older children or because there may be a threshold of exposure below which certain respiratory effects may not be expected to occur. For this latter case, equation 8-1 is not an appropriate model, and the observed relative risk would be taken to be the true risk. Both models are addressed in the sections that follow.

8.4. ASSESSMENT OF RISK

Neither the NRC report (1986) nor the Surgeon General's report (U.S. DHHS, 1986) attempted to assess the population or public health impact of the increased risk of respiratory disorders in children attributable to ETS exposure. In this section, estimates will be derived for the number of ETS-attributable lower respiratory tract infections in infants and for the induction and exacerbation of childhood asthma. Quantifying the public health impact of other conditions, such as reduced lung function, coughing, wheezing, and middle ear effusion, is difficult, either because of the lack of overt symptoms or because some necessary U.S. population health statistics are not available. Estimates of sudden infant death syndrome (SIDS) deaths attributable to ETS will not be made but will be discussed in Section 8.4.3.

For the following quantitative analyses, estimates will be developed in terms of ranges. The ranges are derived by the use of both threshold and nonthreshold (equation 8-1) models, different estimates for population incidence and prevalence, and estimated values of Z and RR from studies reviewed above. Various differences in design, disease definition, and conduct among these studies make them less adaptable to meta-analysis techniques than were the lung cancer studies. To the extent that a less rigorous statistical analysis is attempted here, the ranges should reflect that uncertainty.

8.4.1. Asthma

From the analysis of studies regarding risk for asthma and ETS exposure, it was concluded that passive smoking increases both the number and severity of episodes in asthmatic children. It was further concluded that ETS is a risk factor for new cases among previously asymptomatic children, since the evidence is suggestive, but not conclusive, of a causal association (see Section 7.6). Relative risks for asthma ranged from 1.0 to 2.5 in the studies analyzed, but methodologies

differed considerably among studies, and effects were often found only in children of mothers who smoke heavily. Of the four large studies, totaling over 9,000 children (Burchfiel et al., 1986; Sherman et al., 1990; Weitzman et al., 1990; Martinez et al., 1991b), three showed statistically significant risk estimates ranging from 1.7 to 2.5, with the two largest ratios, 2.5 (Martinez et al., 1991b) and 2.1 (Weitzman et al., 1990), coming from comparisons using children of heavily smoking mothers (≥ 10 cig./day) as the exposed group. The third study (Burchfiel et al., 1986) had OR = 1.7 for males with two smoking parents, but results were not significant either for girls or for children with one parental smoker. The fourth study (Sherman et al., 1990) (770 children) did not find an effect, but made no effort to assess the effect of heavy smoking by parents, nor was there control for socioeconomic status. Thus, assigning a range of 1.75 to 2.25 for the estimated relative risk of developing asthma for children of mothers who smoke 10 or more cigarettes per day appears reasonable and is within the ranges of observed risk.

The above results suggest two possible scenarios. One scenario is that relatively heavy exposure to ETS is needed to bring on asthma, i.e., there is a threshold of exposure below which effects will not occur. Alternatively, lesser exposures may merely induce fewer effects, not detectable statistically with these study designs. The choice of scenario does not affect the observed relative risk but will affect whether or not an adjustment for background exposure (Z ratio) is appropriate. Under the first (threshold) scenario, the estimates of RR = 1.75 to 2.25 need no adjustment; under the alternative (nonthreshold) scenario, equation 8-1 applies.

Considering the nonthreshold model first, from the discussion in Section 8.3, it can be assumed that values of 3 to 10 may be a reasonable range for estimates of Z (i.e., the ratio of body cotinine levels in children whose mothers smoke heavily to those of children whose mothers do not smoke). Lower values of Z would yield significantly larger estimates of asthma cases attributable to ETS. Based on the above estimates for a range of Z and RR and use of the nonthreshold model, the estimated range of adjusted relative risks for children of mothers who smoke 10 or more cigarettes per day would be approximately 1.91 to 6.00 (see Table 8-3). Transforming relative risks to attributable risks (Rothman, 1986), 48% to 83% of all cases of asthma among children of mothers who smoke 10 or more cigarettes per day may be attributable to passive smoking based on

$$AR_E = 100 * (1 - [1/RR]) \qquad (8\text{-}2)$$

where AR_E is the attributable risk (%) for the exposed population.

Under the assumptions of the threshold model, RR = 1.75 to 2.25 for children of heavily smoking mothers, and the AR_E = 43% to 56% (see Table 8-3); for children of light smoking mothers, RR = 1, and the AR_E = 0.

To calculate the percentage of all cases occurring in a mixed population of exposed and unexposed individuals that is attributable to exposure (AR_T), knowledge of the prevalence of mothers smoking 10 or more cigarettes per day is needed because

$$AR_T = AR_E * P_I \qquad (8\text{-}3)$$

where P_I is the proportion of cases that is exposed (Rothman, 1986). It has been reported that approximately 26% of the population of women of childbearing age smoked in the United States in 1988 (CDC, 1991b) and in 1990 (CDC, unpublished). For the number of cigarettes smoked, Weitzman and coworkers (1990), using the 1981 National Health Information Survey (NHIS), found that approximately 50% of smoking mothers of children ages 0 to 5 years smoke 10 or more cigarettes per day. The 1990 NHIS reports that 78% of smoking women ages 18 to 44 smoke at least 10 cigarettes per day (data courtesy of Dr. Gary Giovino, CDC, unpublished). We have used an average of 65% to derive the estimates in Table 8-3. Based on these figures and the threshold model, it can thus be estimated that approximately 7% to 9% of all cases of asthma may be attributable to exposure to ETS from mothers who smoke 10 or more cigarettes per day. Estimates of the prevalence of asthma among U.S. children less than age 18 vary from 5% to 10% (Clark and Godfrey, 1983) to 3% to 8% (R. Evans et al., 1987), depending on disease definition. This latter paper uses the data from the 1979-1981 NHIS and derives a population asthma prevalence of 2 million to 5 million. A more recent estimate from the 1989 NHIS is 3.9 million (U.S. DHHS, 1990b). Use of these population prevalence figures and the threshold model provides a range of 8,000 to 26,000 as the annual number of new cases of childhood asthma attributable to mothers who smoke 10 or more cigarettes per day. The confidence in this estimate is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

If the nonthreshold model applies, use of the same prevalence figures leads to a range of 13,000 to 60,000 new cases per year attributable to all ETS exposures (Table 8-3).

While the range of 8,000 to 60,000 is plausible, the existing data are more supportive of the threshold model, which assumes that rather heavy exposures to ETS are required to induce asthma in previously asymptotic children (Section 7.6.2). Thus, the range of 8,000 to 26,000 will be

adopted as the more probable range of new cases among children per year attributable to ETS exposure.

In view of the increased number and severity of asthmatic episodes also caused by ETS, the public health impact of ETS on asthmatic children is considerably greater than the range of estimates for new cases presented above. Shephard (1992), after reviewing several studies, concludes that ETS exposure (from any source) exacerbates preexisting asthma in approximately 20% of patients. If this figure is correct, up to 1 million asthmatic children could be affected. Also, in an earlier study, O'Connell and Logan (1974) found that parental smoking aggravated clinical symptoms of 67% of 265 asthmatic children in the Midwest versus 16% of 137 controls ($p < 0.0001$) and that 10% of 400 asthmatic patients (of both smoking and nonsmoking parents) considered tobacco smoke a major aggravating factor. D. Evans and coworkers (1987) found that passive smoking by asthmatic children in New York City (via presence of smokers in the household) was associated with a mean annual increase of 1.34 emergency room visits per year for asthmatic symptoms, an increase of 63% over asthmatic children from nonsmoking households. Thus, exposure to ETS in general and especially to parental ETS adversely affects hundreds of thousands of asthmatic children.

8.4.2. Lower Respiratory Illness

From the assessment of available data (see Section 7.3), it was concluded that exposure of infants and young children to ETS causes an increased incidence of lower respiratory illness (LRI). An examination of the data in the referenced studies of both Tables 7-1 and 7-2 leads to the conclusion that the observed risk of having LRIs is approximately 1.5 to 2.0 times as high in young children whose mothers smoke as in those whose mothers do not smoke and that the risk is probably higher in infants than in toddlers.

This estimate is also consistent with that of the NRC (1986), which estimated a relative risk of up to 2 for infants who have one or more parents who smoke. The more recent evidence reviewed here strongly suggests that the increased risk due to ETS exposure lasts for at least the first 18 months and decreases after that. Based on this evidence, this chapter estimates a relative risk range of 1.5 to 2.0 for infants and children up to 18 months old who have smoking mothers. It will assume that the increased risk is zero after 18 months.

Based on these findings, and following equation 8-1 with a range of $Z = 3$ to 10 and $RR = 1.5$ to 2.0, the adjusted relative risk range becomes 1.6 to 4.0, and AR_E takes the range 38% to 75%. As in the previous section, for equation 8-3, the mixed population attributable risk AR_T

takes the range 10% to 20%, again based on 1988 and 1990 estimates of approximately 26% women of childbearing age who smoked (CDC, 1991b; CDC, unpublished). Because the estimated mean number of cigarettes smoked by these women is approximately 17 to 20 per day (CDC 1991b; CDC, unpublished), it is reasonable to assume that most children of smoking mothers will be exposed. Therefore, the proportion of cases exposed, P_1, is estimated to be 0.26.

It has recently been shown that the incidence of LRIs early in life is approximately 30% (Wright, 1991). When the analysis is limited to the first 18 months of life, the population at risk is approximately 5.5 million children. Application of the same algorithms described above yields 150,000 to 300,000 cases of LRIs annually in children under 18 months old attributable to exposure to ETS generated mostly by smoking mothers. Approximately 5% of these LRIs require admission to a hospital (Wright, 1989), and therefore, it is estimated that 7,500 to 15,000 hospitalizations yearly for LRIs may be attributable to ETS exposure.

While these estimates may appear large, three factors suggest that they are on the low side. First, although these estimates are calculated only for children less than 18 months old, Section 7.2 presents evidence that these ETS-attributed increased risks extend at a decreasing rate up to 3 years of age. Second, no estimates have been calculated for exposure in a smoking father-nonsmoking mother household. Third, these numbers do not take into account the fact that many infants and young children have recurrent LRIs, and therefore, more than one episode of such illnesses may be attributable to ETS in each exposed child.

8.4.3. Sudden Infant Death Syndrome

Because this report concludes that there is an association between maternal smoking and SIDS but is unable to determine the contribution that ETS makes to that association (see Section 7.7), no estimate of ETS-attributable SIDS deaths will be calculated. The Centers for Disease Control (CDC) (1991a) provides an estimate of 702 SIDS deaths attributable to maternal smoking, based on a relative risk of 1.5 for infants of actively smoking mothers. While this report concurs with the numbers and the methodology used to determine that estimate, it is unable to apportion the in utero, lactation, and ETS exposure components of the risk.

8.5. CONCLUSIONS

This chapter has attempted to estimate the U.S. population impact of ETS exposure on childhood asthma and lower respiratory tract infections in young children. For new cases of asthma in previously symptomatic children under 18 years of age, we estimate that 8,000 to 26,000

is a probable range of new cases per year that are attributable to ETS exposure from mothers who smoke at least 10 cigarettes per day. The confidence in this range is medium and is dependent on the conclusion that ETS is a risk factor for asthma induction.

While the data are most supportive of a situation in which heavy exposures to ETS are required to induce new cases of asthma, two other scenarios would lead to larger estimates. The first is that even in the absence of smoking mothers, a child could receive heavy ETS exposure from other sources. The second is that lesser ETS exposures induce lesser numbers of new cases, and the increase is not statistically detectable. Under this latter (nonthreshold) scenario, the range of new cases of asthma annually attributable to ETS exposure is 13,000 to 60,000.

This report concludes that, in addition to inducing new cases of asthma, ETS exposure increases the number and severity of episodes among this country's 2 million to 5 million asthmatic children. This chapter considers exposure to parental smoking to be a major aggravating factor to approximately 10%, or 200,000, asthmatic children. Estimates of the number of asthmatics whose condition is aggravated to some degree by ETS exposure are very approximate but could run well over 1 million.

This chapter also estimates that 150,000 to 300,000 cases annually of lower respiratory tract infections in children up to 18 months old are attributable to ETS exposure, most of which comes from smoking parents (mostly mothers). These ETS-attributable cases are estimated to result in 7,500 to 15,000 hospitalizations annually. Confidence in these estimates is high based on the conclusion of a causal association and the strong validity of parental smoking as a surrogate of temporally-relevant ETS exposure in infants and young children. Additional cases and hospitalizations are expected to occur in children up to 3 years old in decreasing numbers, but this report makes no further quantitative estimates.

Infants' exposure to ETS may also be responsible for a portion of the more than 700 deaths from SIDS attributable to maternal smoking by the CDC (1991a), but this report is unable to determine whether and to what extent these deaths can be attributed specifically to ETS exposure.

The estimates of population impact presented above are given in ranges and approximate values to reflect the uncertainty of extrapolating from individual studies to the population. As with the lung cancer population impact assessment (Chapter 6), these extrapolations are all based on human studies conducted at true environmental levels. Therefore, they suffer from none of the uncertainties associated with either animal-to-human or high-to-low exposure extrapolations.

In addition to the estimates presented above, ETS exposure in children also leads to reduced lung function, increased symptoms of respiratory irritation, and increased prevalence of

middle ear effusion, but this report does not provide estimates of the population impact of ETS exposure for these conditions.

Table 8-1. Adjusted relative risks for "exposed children." Adjusted or background exposure based on body cotinine ratios between "exposed" and "unexposed" and equation 8-1

OBSERVED RELATIVE RISKS (RR)	Z RATIO OF BODY COTININE LEVELS ("EXPOSED"/"UNEXPOSED") 1.50	2.00	3.00	5.00	7.00	10.00	13.00	17.00
1.0	1	1	1	1	1	1	1	1
1.50	-	3.00	2.00	1.71	1.64	1.59	1.57	1.55
1.75	-	7.00	2.80	2.15	2.00	1.91	1.87	1.84
2.00	-	-	4.00	2.67	2.40	2.25	2.18	2.13
2.50	-	-	10.00	4.00	3.33	3.00	2.86	2.76
3.00	-	-	-	6.00	4.50	3.86	3.60	3.43

Table 8-2. Behavior variations in adjusted relative risks from equation 8-1 when the observed relative risks and Z ratios are close together

OBSERVED RELATIVE RISKS (RR)	Z RATIO 1.50	1.75	2.00	2.25	2.50	2.75	3.00	10.00
1.50	-	4.50	3.00	2.50	2.25	2.10	2.00	1.59
1.75	-3.5	-	7.00	4.38	3.50	3.06	2.80	1.91
2.00	-2.0	-6.00	-	10.00	6.00	4.67	4.00	2.25
2.25	-1.5	-3.38	-9.00	-	13.50	7.88	6.00	2.62
2.50	-1.25	-2.50	-5.00	-12.50	-	17.50	10.00	3.00

TABLE 8.3 Range of Estimates of Adjusted Relative Risk and Attributable Risk for Asthma Induction in Children ased on Both Threshold[1] and Nonthreshold Models[2]

	Threshold Model[1]		Nonthreshold Model[2]				
Observed Relative Risk	1.75	2.25	1.75	2.25	1.75	2.00	2.25
Adjusted Relative Risk[3]	-	-	1.91+	2.62+	2.80*	4.00*	6.00*
AR_E[4]	0.43	0.56	0.48	0.62	0.64	0.75	0.83
AR_T[5] (P_I[6]=0.17)	0.07	0.09	-	-	-	-	-
AR_T (P_I[7]=0.26)	-	-	0.12	0.16	0.17	0.20	0.22
ETS-Attributable Population Impact[8]	8,000 to 20,000	10,000 to 26,000	13,000 to 34,000	18,000 to 45,000	19,000 to 46,000	22,000 to 54,000	24,000 to 60,000

1. Threshold model assumes that heavy ETS exposure (i.e., mothers smoking $\geq$ 10 cig./day) is required to induce new cases.
2. Nonthreshold model assumes that all ETS exposure can produce some new cases of asthma.
3. Equation 8-1.
4. Attributable risk fraction for the exposed population.
5. Attributable risk fraction for the total (mixed) population.
6. Proportion of women of reproductive age who smoke at least 10 cigarettes per day. (0.26 x 0.65)
7. Proportion of women of reproductive age who smoke cigarettes.
8. Range based on 2 million to 5 million asthmatic children under 18 years old in the United States.

+ Ratio of mean body cotinine levels: Z = 10
* Ratio of mean body cotinine levels: Z = 3

SELECTED BIBLIOGRAPHY

Note: This section includes all references cited in the document as well as additional references that were reviewed during the preparation of this document. This is not intended to be a comprehensive list of all references available on the topic.

Adams, J.D.; O'Mara-Adams, K.J.; Hoffmann, D. (1987) Toxic and carcinogenic agents in undiluted mainstream smoke and sidestream smoke of different types of cigarettes. Carcinogenesis 8(5):729-731.

Aguayo, S.M.; Kane, M.A.; King, T.E.; Schwarz, M.I.; Grauer L.; Miller, Y.E. (1989) Increased levels of bombesin-like peptides in the lower respiratory tract of asymptomatic cigarette smokers. J. Clin. Invest. 84:1105-1113.

Akiba, S.; Kato, H.; Blot, W.J. (1986) Passive smoking and lung cancer among Japanese women. Cancer Res. 46:4804-4807.

Alderson, M.R.; Lee, P.N.; Wang, R. (1985) Risks of lung cancer, chronic bronchitis, ischaemic heart disease and stroke in relation to type of cigarette smoked. J. Epidemiol. Community Health 39:286.

Alfheim, I.; Ramdahl, T. (1984) Contribution of wood combustion to indoor air pollution as measured by mutagenicity in Salmonella and polycyclic aromatic hydrocarbon concentration. Environ. Mol. Mutagen. 6:121-120.

Almanac of the 50 States. (1989) Hornon, E.R., ed. Palo Alto, CA: Information Publications.

American Academy of Pediatrics (1986) (p. 1-7).

Anderson, L.J.; Parker, R.A.; Strikas, R.A.; et al. (1988) Day-care center attendance and hospitalization for lower respiratory tract illness. Pediatrics 82:300-308.

Andrae, S.; Axelson, O.; Bjorksten, B.; Fredriksson, M.; Ljellman, N-IM. (1988) Symptoms of bronchial hyperreactivity and asthma in relation to environmental factors. Arch. Dis. Child. 63:473-478.

Aoki,_; et al. (1987) Smoking and Health. _. Elsevier Science Publishers B.V. (Biomedical Division), pp. 483-486.

Arundel, A.; Sterling, T.; Weinkam, J. (1987) Never smoker lung cancer risks from exposure to particulate tobacco smoke. Environ. Intl. 13:409-426.

Badre, R.; Guillerm, R.; Abran, N.; Bourdin, M.; Dumas, C. (1978) Atmospheric pollution by cigarette smoking. Ann. Pharm. Fr. 36:443-452.

Basrur, P.K.; McClure, S.; Zilkey, B. (1978) A comparison of short term bioassay results with carcinogenicity of experimental cigarettes. In: Nieburgs, H.E., ed. Prevention and detection of cancer, Part 1, Vol. 2, New York: Marcel Dekker, pp. 2041-2048.

Bellofiore, S.; Eidelman, D.H.; Macklem, P.T.; Martin, J.G. (1989) Effects of elastase-induced emphysema on airway responsiveness to methacholine in rats. J. Appl. Physiol. 66:606-612.

Benner, C.L.; Bayona, J.M.; Caka, F.M.; Tang, H.; Lewis, L.D.; Eatough, D.J. (1989) Chemical composition of environmental tobacco smoke. 2. Particle-phase compounds. Environ. Sci. Technol. 23:688-699.

Bergman, A.B.; Wiesner, B.A. (1976) Relationship of passive cigarette-smoking to sudden infant death syndrome. Pediatrics 58:665-668.

Berkey, C.S.; Ware, J.H.; Dockery, D.W.; Ferris, B.G., Jr.; Speizer, F.E. (1986) Indoor air pollution and pulmonary function in preadolescent children. Am. J. Epidemiol. 123:250-260.

Bernfeld, P.; Homburger, F.; Soto, E.; Pai, K.J. (1979) Cigarette smoke inhalation studies in inbred Syrian golden hamsters. J. Natl. Cancer Inst. 63:675-689.

Best, E.W.R.; Josie, G.H.; Walker, C.B. (1961) A Canadian study of mortality in relation to smoking habits. A preliminary report. Can. J. Public Health 52:99-106.

Bewley, B.R.; Halil, T.; Snaith, A.H. (1973) Smoking by primary schoolchildren: prevalence and associated respiratory symptoms. Br. J. Prev. Soc. Med. 27:150-153.

Bisgaard, H.; Dalgaard, P.; Nyboe, J. (1987) Risk factors for wheezing during infancy: a study of 5953 infants. Acta Paediatr. Scand. 76:719-726.

Black, N. (1984) Surgery for glue ear—a modern epidemic? Lancet i:835-837.

Black, N. (1985) The etiology of glue ear—a case-control study. Int. J. Pediatr. Otolaryngol. (Stockholm) 9:121-133.

Bland, M.; Bewley, B.R.; Pollard, V.; Banks, N.M. (1978) Effect of children's and parents' smoking on respiratory symptoms. Arch. Dis. Child. 53:100-105.

Blot, W.J.; Fraumeni, J.F. (1986) Passive smoking and lung cancer. J. Natl. Cancer Inst. 77(5):993-999.

Breese-Hall, C.; Hall, J.H.; Gala, C.L.; MaGill, F.B.; Leddy, J.P. (1984) Long-term prospective study in children after respiratory syncytial virus infection. J. Pediatr. 105:358-364.

Breslow, N.E.; Day, N.E. (1980) Statistical methods in cancer research. Lyon: IARC Sci. Publ. No. 32.

Britten, N. (1988) Validity of claims to lifelong non-smoking at age 36 in a longitudinal study. Int. J. Epidemiol. 17(3):525-529.

Bross, I.D.J.; Gibson, R. (1968) Risk of lung cancer in smokers who switch to filter cigarettes. Am. J. Public Health 58:1396-1403.

Brown, C.C.; Chu, K. (1987) Use of multistage models to infer stage affected by carcinogenic exposure: example of lung cancer and cigarette smoking. J. Chronic Dis. 40(2):171A-179A.

Brownson, R.C.; Reif, J.S.; Keefe, T.J.; Ferguson, S.W.; Pritzl, J.A. (1987) Risk factors for adenocarcinoma of the lung. Am. J. Epidemiol. 125:25-34.

Brunekreef, B.; Boleij, J.S.M. (1982) Long-term average suspended particulate concentrations in smokers' homes. Int. Arch. Occup. Environ. Health 50:299-302.

Brunekreef, B.; Fischer, P.; Remijn, B.; Van der Lende, R.; Schouten, J.; Quanjer, P.H. (1985) Indoor air pollution and its effects on pulmonary function of adult non-smoking women. III. Passive smoking and pulmonary function. Int. J. Epidemiol. 14:227-230.

Brunnemann, K.D.; Hoffmann, D.; Wynder, E.L.; Gori, G.B. (1976) Chemical studies on tobacco smoke: 37. Determination of tar, nicotine, and carbon monoxide in cigarette smoke. A comparison of international smoking conditions. In: Wynder, E.L.; Hoffmann, D; Gori, G.B., eds. Modifying the risk for the smoker: proceedings of the third world conference on smoking and health, DHEW Pub. No. (NIH) 76-1221, New York: June 1975; Vol 1. U.S. Department of Health, Education, and Welfare, National Cancer Institute, pp. 441-449.

Brunnemann, K.D.; Adams, J.D.; Ho, D.P.; Hoffmann D. (1978) The influence of tobacco smoke on indoor atmospheres. II. Volatile and tobacco-specific nitrosamines in main and sidestream smoke and their contribution to indoor pollution: proceedings of the 4th joint conference on sensing of environmental pollutants. Washington, DC: American Chemical Society, pp. 876-880.

Buffler, P.A.; Pickle, L.W.; Mason, T.J.; Contant, C. (1984) The causes of lung cancer in Texas. In: Mizell, M.; Correa, P., eds. Lung cancer: causes and prevention. New York: Verlag Chemie International, pp. 83-99.

Burchfield, C.M.; Higgins, M.W.; Keller, J.B.; Howatt, W.F.; Butler, W.J.; Higgins, I.T.T. (1986) Passive smoking in childhood: respiratory conditions and pulmonary function in Tecumseh, Michigan. Am. Rev. Respir. Dis. 133:966-973.

Burney, P.G.; Britton, J.R.; Chinn, S.; et al. (1987) Descriptive epidemiology of bronchial reactivity in an adult population: results from a community study. Thorax 42:38-44.

Burrows, B.; Halonen, M.; Barbee, R.A.; Lebowitz, M.D. (1981) The relationship of serum immunoglobulin E to cigarette smoking. Am. Rev. Respir. Dis. 124:523-525.

Burrows, B.; Knudson, R.J.; Cline, M.G.; Lebowitz, M.D. (1988) A reexamination of risk factors for ventilatory impairment. Am. Rev. Respir. Dis. 138:829-836.

Burrows, B.; Martinez, F.D.; Halonen, M.; Barbee, R.A.; Cline, M.G. (1989) Association of asthma with serum IgE levels and skin-test reactivity to allergens. N. Engl. J. Med. 320:271-277.

Butler, T.L. (1988) The relationship of passive smoking to various health outcomes among Seventh-Day Adventists in California [dissertation]. Los Angeles: University of California at Los Angeles.

Butler, W.J. (1990) Unpublished comments submitted to EPA on its draft report entitled "Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children," EPA/600/6-90/006A, May, 1990.

Butler, W.J. (1991) Supplementary information on confounding and the reported epidemiologic association between lung cancer and spousal smoking status (unpublished).

Caddeback, J.E.; Donovan, J.R.; Burg, W.R. (1976) Occupational aspects of passive smoking. Am. Ind. Hyg. Assoc. J. 37:263-267.

Cameron, P.; Kostin, J.S.; Oselett, B.; Stocker, R.; Tighe, G.; Winton, J.; Wolfe, J.H.; Zaks, J.M. (1969) The health of smokers' and nonsmokers' children. Journal of Allergy 43(6):336-341.

Camilli, A.E.; Burrows, B.; Knudson, R.J.; Lyle, S.K.; Lebowitz, M.D. (1987) Longitudinal changes in FEV1 in adults: effects of smoking and smoking cessation. Am. Rev. Respir. Dis. 135:794-799.

Cano, J.P.; Catalin, J.; Badre, R.; Dumas, C.; Viala, A.; Guillerme, R. (1970) Determination de la nicotine par chromatographie en phase gazeuse. II. Applications. Ann. Pharm. Fr. 28:633-640.

CDC. *See* Centers for Disease Control.

Cederlof, R.; Friberg, L.; Hrubec, Z.; Lorich, U. (1975) The relationship of smoking and some social covariables in mortality and cancer morbidity: a ten year follow-up on a probability sample of 55,000 Swedish subjects age 18-69, Parts 1 and 2. Stockholm, Sweden: Department of Environmental Hygiene, Karolinska Institute.

Centers for Disease Control. (1989) Chronic disease reports: mortality trends—United States, 1979-1986. MMWR 38:189-191.

Centers for Disease Control. (1989) Years of potential life lost before age 65—United States, 1987. MMWR 38:27-28.

Centers for Disease Control. (1991a) Smoking-attributable mortality and years of potential life lost—United States, 1988. MMWR 40:62-71.

Centers for Disease Control. (1991b) Cigarette smoking among adults—United States, 1988. MMWR 40:757-765.

Chan, W.C.; Fung, S.C. (1982) Lung cancer in non-smokers in Hong Kong. In: Grundmann, E., ed. Cancer campaign, Vol. 6, cancer epidemiology. Stuttgart: Gustav Fischer Verlag, pp. 199-202.

Chan, W.C.; Colbourne, M.J.; Fung, S.C.; Ho, H.C. (1979) Bronchial cancer in Hong Kong, 1976-1977. Br. J. Cancer 39:182-192.

Chan, K.M.; Noble-Jamieson, C.M.; Elliman, A.; Bryan, E.M.; Silverman, M. (1989) Lung function in children of low birth weight. Arch. Dis. Child. 64:1284-1293.

Chan, K.N.; Elliman, A.; Bryan, E.; Silverman, M. (1989) Respiratory symptoms in children of low birth weight. Arch. Dis. Child. 64:1294-1304.

Charlton, A. (1984) Children's coughs related to parental smoking. Brit. Med. J. 288:1647-1649.

Chen, M.F.; Kimisuka, G.; Wang, N.S. (1987) Human fetal lung changes associated with maternal smoking during pregnancy. Pediatr. Pulmonol. 3:51-58.

Chen, Y. (1989) Synergistic effect of passive smoking and artificial feeding on hospitalization for respiratory illness in early childhood. Chest 95:1004-1007.

Chen, Y.; Li, W. (1986) The effect of passive smoking on children's pulmonary function in Shanghai. Am. J. Public Health 76:515-518.

Chen, Y.; Li, W.; Yu, S. (1986) Influence of passive smoking on admissions for respiratory illness in early childhood. Br. Med. J. 293:303-306.

Chen, Y.; Li, W.; Yu, S.; Qian, W. (1988) Chang-Ning epidemiological study of children's health: I Passive smoking and children's respiratory diseases. Int. J. Epidemiol. 17:348-355.

Chilmonczyk, B.A.; Knight, G.J.; Palomaki, G.E.; Pulkkinen, A.J.; Williams, J.; Haddow, J.E. (1990) Environmental tobacco smoke exposure during infancy. Am. J. Public Health 80:1205-1208.

China Map Press. (1979) Atlas of Cancer Mortality in the People's Republic of China.

Clark, T.J.H.; Godfrey, S. (1983) Asthma. 2nd edition. Cambridge, _: Chapman and Hall Medical.

Claxton, L.D.; Morin, R.S.; Huges, T.J.; Lewtas, J. (1989) A genotoxic assessment of environmental tobacco smoke using bacterial bioassays. Mutat. Res. 222:81-99.

Coghlin, J.; Hammond, S.K.; Gann, P. (1989) Development of epidemiologic tools for measuring environmental tobacco smoke exposure. Am. J. Epidemiol. 130:696-704.

Cogswell, J.J.; Mitchel, E.B.; Alexander, J. (1987) Parental smoking, breast feeding, and respiratory infection in development of allergic diseases. Arch. Dis. Child. 62:336-344.

Colley, J.R.T. (1971) Respiratory disease in childhood. Br. Med. Bull. 27:9-14.

Colley, J.R.T. (1974) Respiratory symptoms in children and parental smoking and phlegm production. Br. Med. J. 2:201-204.

Colley, J.R.T.; Holland, W.W.; Corkhill, R.T. (1974) Influence of passive smoking and parental phlegm on pneumonia and bronchitis in early childhood. Lancet 2:1031-1034.

Collier, A.M.; Goldstein, G.M.; Shrewsbury, R.P.; Zhang, C.A.; Williams, R.W. (1990) Urine cotinine elimination half-life in young children exposed to sidestream cigarette smoke. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 195-200.

Collins, M.H.; Moessinger, A.C.; Kleinerman, J.; Bassi, J.; Rosso, P.; Collins, A.M.; James, L.S.; Blanc, W.A. (1985) Fetal lung hypoplasia associated with maternal smoking: a morphometric analysis. Pediatr. Res. 19:408-412.

Comstock, G.W.; Meyer, M.B.; Helsing, K.J.; Tockman, M.S. (1981) The respiratory effects of household exposure to tobacco smoke and gas cooking. Am. Rev. Respir. Dis. 124:143-148.

Corbo, G.M.; Fuciarelli, F.; Foresi, A.; De Benedetto, F. (1989) Snoring in children: association with respiratory symptoms and passive smoking. Br. Med. J. 299:1491-1494.

Correa, P.; Fontham, E.; Pickle, L.; Lin, Y.; Haenszel, W. (1983) Passive smoking and lung cancer. Lancet 2:595-597.

Coultas, D.B.; Howard, C.A.; Peake, G.T.; Skipper, B.J.; Samet, J.M. (1987) Salivary cotinine levels and involuntary tobacco smoke exposure in children and adults in New Mexico. Am. Rev. Respir. Dis. 136:305-309.

Coultas, D.B.; Howard, C.A.; et al. (1988) Discrepancies between self-reported and validated cigarette smoking in a community survey of New Mexico Hispanics. Am. Rev. Respir. Dis. 137:810-814.

Coultas, D.B.; Peake, G.T.; Samet, J.M. (1989) Questionaire assessment of lifetime and recent exposure to environmental tobacco smoke. Am. J. Epidemiol. 130:338-347.

Coultas, D.B.; Samet, J.M.; McCarthy, J.F.; Spengler, J.D. (1990a) A personal monitoring study to assess workplace exposure to environmental tobacco smoke. Am. J. Public Health 80:988-990.

Coultas, D.B.; Samet, J.M.; McCarthy, J.F.; Spengler, J.D. (1990b) Variability of measures of exposure to environmental tobacco smoke in the home. Am. Rev. Respir. Dis. 142:602-606.

Cummings, K.M. (1990) Statement to the U.S. Environmental Protection Agency Science Advisory Board Indoor Air Quality and Total Human Exposure Committee. Environmental Tobacco Smoke Review, December 4, 1990.

Cummings, K.M.; Markello, S.J.; Mahoney, M.C.; Marshall, J.R. (1989) Measurement of lifetime exposure to passive smoke. Am. J. Epidemiol. 130:122-132.

Cummings, K.M.; Markello, S.J.; et al. (1990) Measurement of current exposure to environmental tobacco smoke. Arch. Environ. Health 45:74-79.

Cutz, E.; Chan, W.; Track, N.S. (1981) Bombesin, calcitonin and leuenkephalin immunoreactivity in endocrine cells of the human lung. Experientia (Basel) 37:765-767.

Dagle, G.E.; McDonald, K.E.; Smith, L.G.; Stevens, D.L., Jr. (1978) Pulmonary carcinogenesis in rats given implants of cigarette smoke condensate in beeswax pellets. J. Natl. Cancer Inst. 61:905-910.

Dalager, N.A.; Pickle, L.W.; Mason, T.J.; Correa, P.; Fontham, E.; Stemhagen, A.; Buffler, P.A.; Ziegler, R.G.; Fraumeni, J.F. (1986) The relation of passive smoking to lung cancer. Cancer Res. 46:4808-4811.

Davies, R.F.; Day, T.D. (1969) A study of the comparative carcinogenicity of cigarette and cigar smoke condensate on mouse skin. Br. J. Cancer 23:363-368.

Day, N.E.; Brown, C.C. (1980) Multistage models and primary prevention of cancer. J. Natl. Cancer Inst. 64:977-989.

Dean, G.; Lee, P.N.; Todd, G.F.; Wicken, A.J. (1977) Report on a second retrospective study in North-east England. Part I. Factors related to mortality from lung cancer, bronchitis, heart disease and stroke in Cleveland County, with particular emphasis on the relative risks associated with smoking filter and plain cigarettes. Research Paper 14. London: Tobacco Research Council.

Deaner, R.M.; Trummer, M.J. (1970) Carcinoma of the lung in women. J. Thorac. Cardiovasc. Surg. 59:551-554.

DeMarini, D.M. (1983) Genotoxicity of tobacco smoke and tobacco smoke condensate. Mutat. Res. 114:59-89.

Dijkstra, L.; Houthuijs, D.; Brunekreef, B.; Akkerman, I.; Boleij, J.S.M. (1990) Respiratory health effects of the indoor environment in a population of Dutch children. Am. Rev. Respir. Dis. 142:1172-1178.

Dodge, R. (1982) The effects of indoor pollution on Arizona children. Arch. Environ. Health. 37:151-155.

Doll, R. (1971) The age distribution of cancer. Implication for models of carcinogenesis. J. R. Stat. Soc. A. 134:133-155.

Doll, R.; Hill, A.B. (1964a) Mortality in relation to smoking: ten years' observations of British doctors. Br. Med. J. i:1399-1410.

Doll, R.; Hill, A.B. (1964b) Mortality in relation to smoking: ten years' observations of British doctors. Br. Med. J. i:1460-1467.

Doll, R.; Peto, R. (1976) Mortality in relation to smoking: 20 years' observations on male British doctors. Br. Med. J. ii:1525-1536.

Doll, R.; Peto, R. (1978) Cigarette smoking and bronchial carcinoma: dose and time relationships among regular smokers and lifelong non-smokers. J. Epidemiol. Community Health 32:303-313.

Doll, R.; Hill, A.B.; Kreyberg, L. (1957) The significance of cell type in relation to the aetiology of lung cancer. Br. J. Cancer 11:43-48.

Doll, R.; Gray, R.; Hafner, B.; Peto, R. (1980) Mortality in relation to smoking: 22 years' observations on female British doctors. Br. Med. J. i:967-971.

Dontenwill, W.; Chevalier, H.J.; Harke, H.P.; Lafrenz, U.; Reckzeh, G.; Schneider, B. (1973) Investigations on the effects of chronic cigarette smoke inhalation in Syrian golden hamsters. J. Natl. Cancer Inst. 51:1781-1832.

Dube, M.F.; Green, C.R. (1982) Methods of collection of smoke for analytical purposes. Recent Adv. Tobacco Sci. 8:42-102.

Dupont, W.D.; Plummer, W.D. (1990) Power and sample size calculations: a review and computer program. In: Controlled Clinical Trials, Vol. 11, Elsevier Science Publishing Co., New York, pp. 116-128.

Dutau, G.; Enjaume, C.; Petrus, M.; Darcos, P.; Demeurisse, P.; Rochiccioli, P. (1981) Enquete epidemiologue sur le tabagisme passif des enfants de 0 a 6 ans. Arch. Fr. Pediatr. 38:721-725.

Eatough, D.J.; Benner, C.; Mooney, R.L.; Batholomew, D.; Steiner, D.S.; Hansen, L.D.; Lamb, J.D.; Lewis, E.A. (1986) Gas and particle phase nicotine in environmental tobacco smoke: proceedings of 79th annual meeting of the Air Pollution Control Association, Paper 86-68.5. June 22-27, 1986; Minneapolis, MN.

Eatough, D.J.; Benner, C.L.; Bayona, J.M.; Caka, H.; Tang, H.; Lewis, L.; Lamb, J.D.; Lee, M.L.; Lewis, E.A.; Hansen, L.D. (1989a) Measurement of toxic and related air pollutants. Pittsburgh, PA: Air Pollution Control Association, pp. 132-139.

Eatough, D.J.; Benner, C.L.; Tang, H.; Landon, V.; Richards, G.; Caka, F.M.; Crawford, F.; Lewis, E.A.; Hansen, L.D.; Eatough, N.L. (1989b) The chemical composition of environmental tobacco smoke. III. Identification of conservative tracers of environmental tobacco smoke. Environ. Int. 15:19-28.

Eatough, D.J.; Caka, F.M.; Crawford, J.; Braithwaite, S.; Hansen, L.D.; Lewis, E.A. (1990) Environmental tobacco smoke in commercial aircraft. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2. Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 311-316.

Ekwo, E.; Weinberger, W.M.; Lachenbruch, P.A.; Humtley, W.H. (1983) Relationship of parental smoking and gas cooking to respiratory disease in children. Chest 84:662-668.

Elliot, L.P.; Rowe, D.R. (1975) Air quality during public gatherings. J. Air Pollut. Control Assoc. 25:635-636.

Etzel, R.A.; Greenberg, R.A.; Haley, N.J.; Loda, F.A. (1985) Urinary cotinine excretion in neonates exposed to tobacco smoke products in utero. J. Pediatr. 107:146-148.

Eudy, L.W.; Thorne, F.A.; Heavor, D.L.; Green, C.R.; Ingebrethsen, B.J. (1985) Studies on the vapour-phase distribution of environmental nicotine by selected trapping and detection methods. Presented at: 39th Tobacco Chemists Research Conference; October; Montreal.

Eudy, L.W.; Thomas, F.A.; Heavner, D.L.; Green, C.R.; Ingebrethsen, B.J. (1986) Studies on the vapor-particulate phase distribution of environmental nicotine by selective trapping and detection methods: proceedings of the Air Pollution Control Association 79th annual meeting, June 22-27, pp. 2-14.

Evans, D.; Levison, J.; Feldman, C.H.; et al. (1987) The impact of passive smoking on emergency room visits of urban children with asthma. Am. Rev. Respir. Dis. 135:567-572.

Evans, R.; Mullolly, D.I.; Wilson, R.W.; Gergen, P.J., Rosenberg, H.M.; Grauman, T.S.; Chevarley, F.M.;

Feinlein, M. (1987) National trends in the morbilidity and mortality of asthma in the U.S. Chest 91(6):655-745.

Fergusson, D.M.; Horwood L.J.; Shannon, F.T.; Taylor, B. (1981) Paternal smoking and lower respiratory illness in the first three years of life. J. Epidemiol. Community Health 35:180-184.

Ferris, B.G.; Ware, J.H.; Berkey, C.S.; Dockery, D.W.; Spiro, A.; Speizer, F.E. (1985) Effects of passive smoking on health of children. Environ. Health Perspect. 62:289-295.

Feyerabend, C.; Higenbottam, T.; Russell, M.A.H. (1982) Nicotinic concentrations in urine and saliva of smokers and nonsmokers. Brit Med J 284:1002-04.

Fielding, J.E. (1985) Smoking: health effects and control (Part I). N. Engl. J. Med. 313:491.

Fiore, M.C.; Novotny, T.E.; Pierce, J.P.; Hatziandreu, E.J.; Patel, K.M.; Davis, R.M. (1989) Trend in cigarette smoking in the United States. The changing influence of gender and race. JAMA 261:49-55.

First, M.W. (1984) Environmental tobacco smoke measurements: retrospect and prospect. Eur. J. Respir. Dis. 65 (Suppl. 133):9-16.

Fleming, D.W.; Cochi, S.L.; Hightower, A.W.; Broome, C.V. (1987) Childhood upper respiratory tract infections: to what degree is incidence affected by day-care attendance? Pediatrics 79:55-60.

Floderus, B.; Cederlof, R.; Friberg, L. (1988) Smoking and mortality: a 21-year follow-up based on the Swedish Twin Registry. Int. J. Epidemiol. 17(2):322.

Fontham, E.T.H.; Correa, P.; Wu-Williams, A.; Reynolds, P.; Greenberg, R.S.; Buffler, P.A.; Chen, V.W.; Boyd, P.; Alterman, T.; Austin, D.F.; Liff, J.; Greenberg, S.D. (November 1991) Lung cancer in nonsmoking women: a multicenter case-control study. Cancer Epidemiol. Biomarkers and Prev., Vol. 1:1, pp. 35-44.

Fraser, G.E.; Beeson, W.L., and Phillips, R.L. (1991) Diet and lung cancer in California Seventh Day Adventists. Am J Epidemiol 133:683-93.

Freedman, D.A.; Navidi, W. (1987a) On the multistage model for carcinogenesis. Tech. Report. No. 47, University of California.

Freedman, D.A.; Navidi, W. (1987b) On the risk of lung cancer for ex-smokers. Tech. Report. No. 135, University of California.

Friedman, G.D.; Petitti, D.B.; Bawol, R.D. (1983) Prevalence and correlates of passive smoking. Am. J. Public Health 73:401-_______.

Gaffney, M.; Altshuler, B. (1988) Examination of the role of cigarette smoke in lung carcinogenesis using multistage models. J. Natl. Cancer Inst. 80:925-931.

Gairola, C. (1982) Genetic effects of fresh cigarette smoke in Saccharomyces cerevisiae. Mutat. Res. 102:123-136.

Gao, Y.; Blot, W.J.; Zheng, W.; Ershow, A.G.; Hsu, C.W.; Levin, L.I.; Zhang, R.; Fraumeni, J.F. (1987) Lung cancer among Chinese women. Intl. J. Cancer 40:604-609.

Garfinkel, L. (1981) Time trends in lung cancer mortality among nonsmokers and a note on passive smoking. J. Natl. Cancer Inst. 6:1061-1066.

Garfinkel, L. (1984) Passive smoking and cancer: American experience. Prev. Med. 13:691-697.

Garfinkel, L.; Silverberg, E. (1991) Lung cancer and smoking trends in the United States over the past 25 years. CA 41:137-145.

Garfinkel, L.; Stellman, S.D. (1988) Smoking and lung cancer in women: findings in a prospective study. Cancer Res. 48:6951-6955.

Garfinkel, L. (1985) Selection, follow-up, and analysis in the American Cancer Society Prospective Studies. Presented at a workshop on the selection, follow-up, and analysis in prospective studies held at the Waldorf-Astoria Hotel, October 3-5, 1983; New York.

Garfinkel, L.; Auerbach, O.; Joubert, L. (1985) Involuntary smoking and lung cancer: a case-control study. J. Natl. Cancer Inst. 75:463-469.

Geller-Bernstein, B.; Kenett, R.; Weisglass, L.; Tsur, S.; Lahav, M.; Levin, S. (1987) Atopic babies with wheezy bronchitis. Allergy 42:85-91.

Geng, G.; Liang, Z.H.; Zhang, G.L. (1988) On the relationship between smoking and female lung cancer. Smoking and Health, Elsevier Science Publishers, pp. 483-486.

Geng, G.; Liang, Z-H; et al. Effects of smoking and passive smoking on female lung cancer in Tianjin area. Tianjin, People's Republic of China: Dept. of Epidemiol., Tianjin Med. Col.

Gerrard, J.W.; Helner, D.C.; Ko, C.G.; Mink, J.; Meyers, A.; Dosman, J.A. (1980) Immunoglobulin levels in smokers and non-smokers. Ann. Allergy 44:261-262.

Gillis, C.R.; Hole, D.J.; Hawthorne, V.M.; Boyle, P. (1984) The effect of environmental tobacco smoke in two urban communities in the west of Scotland. Eur. J. Respir. Dis. 133(Suppl.):121-126.

Glantz, S.A.; Parmley, W.W. (1991) Passive smoking and heart disease. Circulation 83:1-12.

Goldstein, G.M.; Collier, A.; Etzel, R.; Lewtas, J.; Haley, N. (1987) Elimination of urinary cotinine in children exposed to known levels of side-stream cigarette smoke. In: Seifert, H.; Esdorn, M.; Fischer, H.; Ruden, J.; Wegner, eds. Indoor air '87, Vol. 2, B. Berlin: Oraniendruck GmbH, pp. 61-67.

Gortmaker, S.L.; Walker, D.K.; Jacobs, F.H.; Ruch-Ross, H. (1982) Parental smoking and the risk of childhood asthma. Am. J. Pub Health 72:572-579.

Graham, N.M.H.; Woodward, A.J.; Ryan, P.; Douglas, R.M. (1990) Acute respiratory illness in Adelaide children. II: The relationship of maternal stress, social supports and family functioning. Int. J. Epidemiol. 19:937-944.

Greenberg, R.A.; Haley, N.J.; Etzel, R.A.; Loda, F.A. (1984) Measuring the exposure of infants to tobacco smoke. N. Engl. J. Med. 310:1075-1078.

Greenberg, R.A.; Bauman, K.E.; Glover, L.H.; Strechar, V.J.; Kleinbaum, D.G.; Haley, N.J.; Stedman, H.C.; Fowler, M.G.; Loda, F.A. (1989) Ecology of passive smoking by young infants. J. Pediatr. 114:774-780.

Greenberg, R.A.; Bauman, K.E.; Strecher, V.J.; Keyes, L.L.; Glover, L.H.; Haley, N.J.; Stedman, H.C.; Loda, F.A. (1991) Passive smoking during the first year of life. Am. J. Public Health 81:850-853.

Greenland, S. (1987) Quantitative methods in the review of epidemiologic literature. Epidem Rev 9:1-30.

Grimmer, G.; Brune, H.; Dettbarn, G.; Naujack, K.-W.; Mohr, U.; Wenzel-Hartung, R. (1988) Contribution of polycyclic aromatic compounds to the carcinogenicity of sidestream smoke of cigarettes evaluated by implantation into the lungs of rats. Cancer Lett. 43:173-177.

Guerin, M. (1987) Formation and physicochemical nature of sidestream smoke. In: O'Neill, I.K.; Brunnemann, K.D.; Dodet, B.; Hoffmann, D., eds. Environmental carcinogens—selected methods of analysis, v. 9, passive smoking. IARC Monographs No. 81. Lyon, France: International Agency for Research on Cancer.

Guerin, M.R.; Jenkins, R.A.; Tomkins, B.A. (1992) The chemistry of environmental tobacco smoke: Composition and measurement. Lewis Publishers, Chelsea, MI.

Gwinn, J.V.; Martinez, F.D.; Wright, A.L.; Ray, C.G.; Taussig, L.M. (1991) Etiology and symptomatology of lower respiratory illnesses (LRIs) in the first three years of life. Am. Rev. Respir. Dis. 143:A509.

Haddow, J.E.; Palomaki, G.E.; Knight, G.J. (1986) Use of serum cotinine to assess the accuracy of self-reported non-smoking. Br. Med. J. 293:1306.

Haddow, J.E.; Knight, G.J.; et al. (1987) Cigarette consumption and serum cotinine in relation to birthweight. Br. J. Obstet. Gynaecol. 94:678-681.

Haddow, J.E.; Knight, G.J.; Palomaki, G.E.; et al. (1988) Second-trimester serum cotinine levels in nonsmokers in relation to birth weight. Am. J. Obstet. Gynecol. 159:481-484.

Haenszel, W.; Taeuber, K.E. (1964) Lung-cancer mortality as related to residence and smoking histories. II. White females. J. Natl. Cancer Inst. 32:803-838.

Haglund, B.; Cnattingius, S. (1990) Cigarette smoking as a risk factor for sudden infant death syndrome: a population-based study. Am. J. Public Health 80:29-32.

Haley, N.J.; Colosimo, S.G.; Axelrad, C.M.; Harris, R.; Sepkovic, D.W. (1989) Biochemical validation of self-reported exposure to environmental tobacco smoke. Environ. Res. 49:127-135.

Halonen, M.; Barbee, R.A.; Lebowitz, M.D.; Burrows, B. (1982) An epidemiologic study of the interrelationships of total serum immunoglobulin E, allergy skin-test reactivity, and eosinophilia. J. Allergy Clin. Immunol. 69:221-228.

Halonen, M.; Stern, D.; Lyle, S.; Wright, A.; Taussig, L.; Martinez, F.D. (1991) Relationship of total serum IgE levels in cord and 9-month sera of infants. Clin. Exp. Allergy 21:235-241.

Hammond, E.C. (1966) Smoking in relation to the death rates of one million men and women. In: Haenszel, W., ed. Epidemiological approaches to the study of cancer and other chronic diseases. National Cancer Institute Monograph No. 19, Washington, DC: pp. 127-204.

Hammond, E.C.; Horn, D. (1958a) Smoking and death rates: report on forty-four months of follow-up of 187,783 men. I. Total mortality. JAMA 166:1159-1172.

Hammond, E.C.; Horn, D. (1958b) Smoking and death rates: report on forty-four months of follow-up of 187,783 men. II. Death rates by cause. JAMA 166:1294-1308.

Hammond, S.K.; Leaderer, B.P. (1987) A diffusion monitor to measure exposure to passive smoking. Environ. Sci. and Technol. 21:494-497.

Hammond, E.C.; Seidman, H. (1980) Smoking and cancer in the United States. Prev. Med. 9:169-173.

Hammond, E.C.; Selikoff, I.J. (1981) Commentary: passive smoking and lung cancer with comments on two new papers. Environ. Res. 24:444-452.

Hammond, S.K.; Leaderer, B.P.; Roche, A.C.; Schenker, M. (1987) Collection and analysis of nicotine as a marker for environmental tobacco smoke. Atmos. Environ. 21:457-462.

Hammond, S.K.; Smith, T.J.; Woskie, S.R.; Leaderer, B.P.; Bettinger, N. (1988) Markers of exposure to diesel exhaust and cigarette smoke in railroad workers. Am. Ind. Hyg. Assoc. J. 49:516-522.

Hammond, S.K.; Lewtas, J.; Mumford, J.; Henderson, J.; Henderson, F.W. (1989) Exposures to environmental tobacco smoke in homes. In: Measurement of toxic and related air pollutants, Environmental Protection Agency/Air and Waste Management Association international symposium, Pittsburgh, PA: Air and Waste Management Association, pp. 590-595.

Hammond, S.K.; Gann, P.H.; Coughlin, J.; Tannenbaum, S.R.; Skipper, P.L. (1990) Tobacco smoke exposure and carcinogen-hemoglobin adducts. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air, Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 157-161.

Hanbury, W.J. (1964) Bronchogenic carcinoma in women. Thorax 19:338-342.

Hanrahan, J.P.; Tager, I.B.; Segal, M.R.; et al. (1990) Effect of prenatal smoking on infant lung function. Am. Rev. Respir. Dis. 141:A282.

Hanson, B.; McGue, M.; Roitman-Johnson, B.; Segal, N.L.; Bouchard, T.J.; Blumenthal, M.N. (1991) Atopic disease and immunoglobulin E in twins reared apart and together. Am. J. Hum. Genet. 48:873-879.

Harmsen, H.; Effenberger, E. (1957) Tobacco smoke in public transportation, dwellings and work rooms. Arch. Hug. 141:383-400.

Hasselblad, V.; Humble, C.G.; Graham, M.G.; Anderson, H. (1981) Indoor environmental determinants of lung function in children. Am. Rev. Respir. Dis. 123:479-485.

Hawthorne, A.R.; Gammage, D.; Dudney, C.S.; Hingerty, B.E.; Schuresko, D.D.; Parzyek, D.C.; Womak, D.R.; Morris, S.A.; Westeley, R.R.; White, D.A.; Schrimscher, J.M. (1984) Air indoor quality study of forty east Tennessee homes. ORNL 5965. Oak Ridge, TN: Oak Ridge National Laboratory, pp. 134.

Hawthorne, V.M.; Fry, J.S. (1978) Smoking and health: the association between smoking behaviour, total mortality and cardiorespiratory disease in West Central Scotland. J. Epidemiol. Community Health 32:260-266.

Higgins, C.E. (1987) Organic vapor phase composition of sidestream and environmental tobacco smoke from cigarettes: Proceedings of the Environmental Protection Agency/Air Pollution Control Association symposium on measurement of toxic and related air pollutants, pp. 140-151.

Hill, A.B. (1953) Observation and experiment. N. Engl. J. Med. 248:995-1001.

Hill, A.B. (1965) The environment and disease: association or causation? proceedings of the Royal Society of Medicine 58:295-300.

Hinds, W.C.; First, M.W. (1975) Concentrations of nicotine and tobacco smoke in public places. N. Engl. J. Med. 292:844-845.

Hinton, A.E. (1989) Surgery for otitis media with effusion in children and its relationship to parental smoking. J. Laryngol. Otol. 103:559-561.

Hirayama, T. (1967) Smoking in relation to the death rates of 265,118 men and women in Japan. Tokyo: National Cancer Center Research Institute.

Hirayama, T. (1975a) Smoking and cancer: a prospective study on cancer epidemiology based on a census population in Japan. In: Steinfeld, J.; Griffiths, W.; Ball, K.; et al., eds. Proceedings of the 3rd world conference on smoking and health, Vol. II, Washington, DC: U.S. Department of Health, Education, and Welfare, pp. 65-72.

Hirayama, T. (1975b) Prospective studies on cancer epidemiology based on a census population in Japan. In: Bucalossi, P.; Veronesi, U.; Cascinelli, N., eds. Proceedings of the XIth international cancer congress, Florence, Italy, 1974, Vol. 3, Cancer epidemiology, environmental factors. Amsterdam: Excerpta Medica, pp. 26-35.

Hirayama, T. (1977) Epidemiology of lung cancer based on population studies. In: National Cancer Center Library, ed. Collected papers from the National Cancer Center Research Institute, Vol. 12. Tokyo: National Cancer Center, pp. 452-461.

Hirayama, T. (1978) Prospective studies on cancer epidemiology based on census population in Japan. In: Nieburgs, H.E., ed. Prevention and detection of cancer, Vol. 1, Etiology. New York: Marcel Dekker, pp. 1139-1147.

Hirayama, T. (1981a) Non-smoking wives of heavy smokers have a higher risk of lung cancer: a study from Japan. Br. Med. J. 282:183-185.

Hirayama, T. (1981b) [Letter] Br. Med. J. 283:916-917.

Hirayama, T. (1982) Smoking and cancer in Japan. A prospective study on cancer epidemiology based on census population in Japan. Results of 13 years follow up. In: Tominaga, S.; Aoki,

K., eds. The UICC smoking control workshop, Nagoya, Japan, August 24-25, 1981. Nagoya: University of Nagoya Press, pp. 2-8.

Hirayama, T. (1983a) Passive smoking and lung cancer: consistency of association. Lancet 2:1425-1426.

Hirayama, T. (1983b) Passive smoking and lung cancer. Presented at the 5th world conference on smoking and health, Winnipeg, Canada.

Hirayama, T. (1984) Cancer mortality in nonsmoking women with smoking husbands based on a large-scale cohort study in Japan. Prev. Med. 13:680-690.

Hirayama, T. (1985) A cohort study on cancer in Japan. In: Blot, W.J.; Hirayama, T.; Hoel, D.G., eds. Statistical methods in cancer epidemiology. Hiroshima: Radiation Effects Research Foundation, pp. 73-91.

Hirayama, T. (1988) Duration of exposure as a determinant of lung cancer risk in passive smokers. Environ. Tech. L. 9:731-732.

Hirayama, T. (1989) Dietary habits are of limited importance in influencing the lung cancer risk among Japanese females who never smoked. In: Bieva, D.J.; Courtois, Y.; Govaerts, M., eds. Present and future of indoor air quality. New York: Elsevier.

Hirayama, T. (1990) Passive smoking and cancer: the association between husbands' smoking and cancer in the lung of non-smoking wives. In: Kaskuga, H., ed. ________________ Berlin: Springer-Verlag.

Hoegg, U.R. (1972) Cigarette smoke in closed spaces. Environ. Health Perspect. 2:117-128.

Hoffman, H.J.; Damus, K.; Hillman, L.; Krongrad, E. (1988) Risk factors for SIDS. Results of the National Institute of Child Health and Human Development SIDS Cooperative Epidemiological Study. Ann. N.Y. Acad. Sci. 533:13-30.

Hoffmann, D.; Hecht, S.S. (1989) Advances in tobacco carcinogenesis. In: Springer handbook of experimental pharmacology: chemical carcinogenesis and mutagenesis (in press).

Hoffmann, D.; Wynder, E.L. (1971) A study of tobacco carcinogenesis. XI. Tumor initiators, tumor accelerators, and tumor promoting activity of condensate fractions. Cancer 27:848-864.

Hoffmann, D.; Haley, N.J.; Adams, J.D.; Brunnemann, K.D. (1984) Tobacco sidestream smoke. Uptake by nonsmokers. Prev. Med. 13:608-617.

Hoffmann, D.; Brunnemann, K.D.; Haley, N.J. (1989) Absorption of smoke constituents by nonsmokers. In: Reducing workplace exposures to environmental tobacco smoke. EPA/HHS Manual.

Hole, D.J; Gillis, C.R.; Chopra, C.; Hawthorne, V.M. (1989) Passive smoking and cardiorespiratory health in a general population in the west of Scotland. Br. Med. J. 299:423-427.

Hopp, R.J.; Bewtra, A.; Nair, N.M.; Townley, R.G. (1985) The effect of age on methacholine response. J. Allergy Clin. Immunol. 76:609-613.

Hopp, R.J.; Townlwy, R.G.; Biven, R.E.; Bewtra, A.K.; Nair, N.M. (1990) The presence of airway reactivity before the development of asthma. Am. Rev. Respir. Dis. 141:2-8.

Hoppenbrouwers, T.; Ceeb, M.; Arakawa, K.; Hodgman, J.E. (1981) Seasonal relationship of sudden infant death syndrome and environmental pollutants. Am. J. Epidemiol. 113:623-635.

Hornon, E.R. (ed) Almanac of the 50 States. Information Publications, Palo Alto, California.

Horwood, L.J.; Fergusson, D.M.; Shannon, F.T. (1985) Social and familial factors in the development of early chilhood asthma. Pediatrics 75:859-868.

Humble, C.G.; Samat, J.M.; Pathak, D.R.; Skipper, B.J. (1985) Cigarette smoking and lung cancer in 'Hispanic' whites and other whites in New Mexico. Am J Public Health 75:145-8.

Humble, C.G.; Samet, J.M.; Pathak, D.R. (1987) Marriage to a smoker and lung cancer risk. Am. J. Public Health 77:598-602.

Husgafvel-Pursiainen, K.; Sorsa, M.; Moller, M.; Benestad, C. (1986) Genotoxicity and polynuclear aromatic hydrocarbon analysis of environmental tobacco smoke samples from restaurants. Mutagenesis 1:287-291.

IARC. *See* International Agency for Research on Cancer.

Idle, J.R. (1990) Titrating exposure to tobacco smoke using cotinine--a minefield of misunderstandings. J. Clin. Epidemiol. 43:313-317.

Inoue, R.; Hirayama, T. (1988) Passive smoking and lung cancer in women. In: Smoking and health. Elsevier Science Publishers, pp. 283-285.

International Agency for Research on Cancer. (1986) IARC monographs on the evaluation of the carcinogenic risk of chemicals to man. Vol. 38. Tobacco smoking. Lyon, France: World Health Organization.

International Agency for Research on Cancer. (1987) Environmental carcinogens—methods of analysis and exposure measurement. Vol. 9: Passive smoking. O'Neill, I.K.; Brunnemann, K.D.; Dodet, B.; Hoffmann, D. eds. Lyon, France: IARC Scientific Publications No. 81.

Ishizu, Y. (1980) General equation or the estimation of indoor pollution. Environ. Sci. Technol. 14:1254-1257.

Iversen, M.; Birch, L.; Lundqvist, G.R.; Elbrond, O. (1985) Middle ear effusion and the indoor environment. Arch. Environ. Health 40:74-79.

Janerich, D.T.; Thompson, W.D.; Varela, L.R.; et al. (1990) Lung cancer and exposure to tobacco smoke in the household. N. Engl. J. Med. 323:632-636.

Jarvis, M.J. (1987) Uptake of environmental tobacco smoke. IARC Sci. Publ. 81:43-58.

Jarvis, M.J. (1989) Application of biochemical intake markers to passive smoking measurement and risk estimation. Mutat. Res. 222:101-110.

Jarvis, M.J.; Russell, M.H.; Feyerabend, C. (1983) Absorption of nicotine and carbon dioxide from passive smoking under natural conditions of exposure. Thorax 38:829-833.

Jarvis, M.; Tunstall-Pedoe, H.; Feyerabend, C.; Vesey, C.; Kabat, G.C.; Wynder, E.L. (1984) Lung cancer in nonsmokers. Cancer 53:1214-1221.

Jarvis, M.J.; Russell, M.A.H.; Feyerabend, C.; Eiser, J.R.; Morgan, M.; Gammage, P.; Gray, E.M. (1985) Passive exposure to tobacco smoke: saliva cotinine concentrations in a representative sample of non-smoking children. Br. Med. J. 291:927-929.

Joly, O.G.; Lubin, J.H.; Caraballoso, M. (1983) Dark tobacco and lung cancer in Cuba. J. Natl. Cancer Inst. 70:1033-1039.

Kabat, G.C. (1990) Epidemiologic studies of the relationship between passive smoking and lung cancer. Presented at the 1990 annual winter meeting of the Toxicology Forum in Washington, DC.

Kabat, G.C.; Wynder, E.L. (1984) Lung cancer in nonsmokers. Cancer 53:1214-1221.

Kabat, G.C.; Wynder, E.L. (1984) Lung cancer in nonsmokers. Cancer 53:1214-1221.

Kahn, H.A. (1966) The Dorn study of smoking and mortality among U.S. veterans: report on eight and one-half years of observation. In: Haenszel, W., ed. Epidemiological approaches to the study of cancer and other chronic diseases. National Cancer Institute Monograph No. 19, Washington, DC, pp. 1-125.

Kalandidi, A.; Trichopoulos, D.; Hatzakis, A.; Tzannes, S.; Saracci, R. (1987) Passive smoking and chronic obstructive lung disease. Lancet ii:1325-1326.

Kalandidi, A; Katsouyanni, K.; Voropoulou, N.; et al. (1990) Passive smoking and diet in the etiology of lung cancer among non-smokers. Cancer Causes and Control 1:15-21.

Kaplan, H.S.; Tsuchitani, P.J. (eds) (1978) Cancer in China, Alan R. Liss, Inc., New York, 1978.

Kasuga, H.; Hasebe, A.; Osaka, F.; Matuski, H. (1979) Respiratory symptoms in school children and the role of passive smoking. Tokai J. Exp. Clin. Med. 4:101-104.

Katada, H.; Mikami, R.; Konishi, M.; Koyama, Y.; Narita, N. (1988) Effect of passive smoking in lung cancer development in women in the Nara region. Gan No Rinsho 34(1):21-27.

Katsouyanni, K.; Kogevinas, M.; Dontas, N.; Maisonneuve, P.; Boyle, P.; Trichopoulos, D. (1990) Mortality from malignant neoplasms in Greece 1960-1985. Greek Cancer Society, Athens, pp. 1-125 [in Greek].

Katz, D.; Baptista, J.; Azen, S.P.; Pike, M.C. Obtaining confidence intervals for the risk ratio in cohort studies. Biometrics 78:469-474.

Kauffmann, F.; Tessier, J.F.; Oriol, P. (1983) Adult passive smoking in the home environment: a risk factor for chronic airflow limitation. Am. J. Epidemiol. 117:269-280.

Kauffmann, F.; Neukirch, F.; Orobaeff, M.; Marne, M.J.; Claud, J.R.; Lellouch, J. (1986) Eosinophils, smoking, and lung function. An epidemiologic survey among 912 working men. Am. Rev. Respir. Dis. 134:1172-1175.

Kauffmann, F.; Dockery, D.W.; Speizer, F.E.; Ferris, B.G. (1989a) Respiratory symptoms and lung function in relation to passive smoking: a comparative study of American and French Women. Int. J. Epidemiol. 18:334-344.

Kauffmann, F.; Tager, I.B.; Munoz, A.; Speizer, F.E. (1989b) Familial factors related to lung function in children aged 6-10 years: results from the PAARC epidemiologic study. Am. J. Epidemiol. 129:1289-1299.

Kentner, M.; Triebig, G.; Weltle, D. (1984) The influence of passive smoking on pulmonary function: a study of 1351 office workers. Prev. Med. 13:656-69.

Kleinbaum, D.G.; Kupper, L.L.; Morgenstern, H. Epidemiologic Research, Lifetime Learning Publications, Belmont, California, 1982.

Knoth, A.; Bohn, H.; Schmidt, F. (1983) Passive smoking as a causal factor of bronchial carcinoma in female nonsmokers. Med. Klin. 78:66-69.

Koo, L.C. (1988) Dietary habits and lung cancer risk among Chinese females in Hong Kong who never smoked. Nutr. Cancer 11:155-172.

Koo, L.C. (1989) Environmental tobacco smoke and lung cancer: is it the smoke or the diet? Elsevier Science Publishers.

Koo, L.C.; Ho, J.H-C.; Saw, D. (1983) Active and passive smoking among female lung cancer patients in Hong Kong. J. Exp. Clin. Cancer Res. 4:367-375.

Koo, L.C.; Ho, J.H-C.; Saw, D. (1984) Is passive smoking an added risk factor for lung cancer in Chinese women? J. Exp. Clin. Cancer Res. 3:277-283.

Koo, L.C.; Ho, J.H-C.; Lee, N. (1985) An analysis of some risk factors for lung cancer in Hong Kong. Int. J. Cancer 35:149-155.

Koo, L.C., Ho, J.H.; Saw, D.; Ho, C.Y. (1987) Measurements of passive smoking and estimates of lung cancer risk among non-smoking Chinese females. Int J Cancer 39:162-169.

Koo, L.C.; Ho, J. H-C.; Rylander, R. (1988b) Life-history correlates of environmental tobacco smoke: a study on nonsmoking Hong Kong Chinese wives with smoking versus nonsmoking husbands. Soc. Sci. Med. 26(7):751-760.

Koutrakis, P.; Fasano, A.M.; Slater, J.L.; Spengler, J.D.; McCarthy, J.F.; Leaderer, B.P. (1989) Atmos. Environ. 23:2767-2773.

Kraemer, M.J.; Richardson, M.A.; Weiss, N.S.; et al. (1983) Risk factors for persistent middle-ear effusions: otitis media, cattarah, cigarette smoke exposure, and atopy. JAMA 249:1022-1025.

Krall, E.A.; Valadian, I.; Dwyer, J.T.; Gardner, J. (1989) Accuracy of recalled smoking data. Am J Publ Health 79:200.

Krzyzanowski, M.; Quackenboss, J.J.; Lebowitz, M.D. (1990) Chronic respiratory effects of indoor formaldehyde exposure. Environ. Res. 52:117-125.

Kuller, L.H.; Garfinkel, L.; Correa, P.; Haley, N.; Hoffmann, D.; Preston-Martin, S.; Sandler, D. (1986) Contribution of passive smoking to respiratory cancer. Environ. Health Perspect. 70:57-69.

Kurihara, M.; Aoki, K.; Miller, R.W.; Muir, C.S. (eds) Changing Cancer Patterns and Topics in Cancer Epidemiology, Plenum Press, New York, 1989.

Lam, W.K. (1985) A clinical and epidemiological study of carcinoma of lung in Hong Kong [doctoral thesis]. Hong Kong: University of Hong Kong.

Lam, T. H.; Kung, I.T.M.; Wong, C.M.; Lam, W.K.; Kleevens, J.W.L.; Saw, D.; Hsu, C.; Seneviratne, S.; Lam, S.Y.; Lo, K.K.; Chan, W.C. (1987) Smoking, passive smoking and histological types in lung cancer in Hong Kong Chinese women. Br. J. Cancer 6:673-678.

Layard, M.W.; Viren, J.R. (1989) Assessing the validity of a Japanese cohort study. Elsevier Science Publishers B.V. (Biomedical Division).

Leaderer, B.P. (1988) Measuring exposure to environmental tobacco smoke. Report prepared for the U. S. Environmental Protection Agency.

Leaderer, B.P. (1989) Unpublished data.

Leaderer, B. (1990) Assessing exposure to environmental tobacco smoke. Risk Anal. 10(1):19-26.

Leaderer, B.P.; Hammond, S.K. (1991) Evaluation of vapor-phase nicotine and respirable suspended particle mass as markers for environmental tobacco smoke. Environ. Sci. Technol. 25(4):770-777.

Leaderer, B.P.; Cain, W.S.; Isseroff, R.; Berglund, L.G. (1984) Ventilation requirements in buildings II. Particulate matter and carbon monoxide from cigarette smoking. Atmos. Environ. 18:99-106.

Leaderer, B.P.; Koutrakis, P.; Briggs, S.; Rizzuto, J. (1990) Impact of indoor sources on residential and concentrations. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 269-274.

Lebowitz, M.D. (1984) The effects of environmental tobacco smoke exposure and gas stoves on daily peak flow rates in asthmatic and non-asthmatic families. Eur. J. Respir. Dig. 133:190-195.

Lebowitz, M.D.; Burrows, B. (1976) Respiratory symptoms related to smoking habits of family adults. Chest 69:49-50.

Lebowitz, M.D.; Holberg, C.J. (1988) Effects of parental smoking and other risk factors on the development of pulmonary function in children and adolescents. Analysis of two longitudinal population studies. Am. J. Epidemiol. 128:589-597.

Lebowitz, M.D.; Holberg, C.J.; Knudson, R.J.; Burrows, B. (1987) Longitudinal study of pulmonary function development in childhood, adolescence, and early adulthood. Am. Rev. Respir. Dis. 136:69-75.

Lebowitz, M.D.; Quackenboss, J.J. (1990) The effect of environmental tobacco smoke on pulmonary function. Int. Arch. Occup. Environ. Health (Suppl):147-152.

Lebret, E.; Boley, J.; Brumekreef, B. (1990) Environmental tobacco smoke in Dutch homes. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and

climate, July 29-August 3. Vol. 2: Characteristics of indoor air, Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 263-268.

Lee, P.N. (1986) Does breathing other people's tobacco smoke cause lung cancer? [Letter] Br. Med. J. 293:1503-1504.

Lee, P.N. (1987a) Lung cancer and passive smoking: association an artifact due to misclassification of smoking habits. Toxicol. Lett. 35:157-162.

Lee, P.N. (1987b) Passive smoking and lung cancer association: a result of bias? Hum. Toxicol. 6:517-524.

Lee, P.N. (1988) Misclassification of smoking habits and passive smoking. Berlin: Springer.

Lee, P.N. (1989) Passive smoking and lung cancer: fact or fiction. In: Bieva, C.J.; Courtois, Y.; Govaerts, M., eds. Present and Future of Indoor Air Quality, Excerpta Medica, Amsterdam, pp. 119-128.

Lee, P.N. (1990) A detailed review of epidemiological evidence relating environmental tobacco smoke (ETS) to the risk of cancer, heart disease and other causes of death in adults who have never smoked. Draft 3 of Annex A.

Lee, P.N. (1991) Correcting meta-analyses of the association of lung cancer in females with spouse (or household) exposure for bias due to misclassification of active smoking status. Submitted to U>S. EPA, dated November 29, 1991.

Lee, P.N.; Chamberlain, J.; Alderson, M.R. (1986) Relationship of passive smoking to risk of lung cancer and other smoking-associated diseases. Br. J. Cancer 54:97-105.

Lee, B.L.; Benowitz, N.L.; Jacob P. (1987) Influence of tobacco abstinence of the disposition kinetics and effects of nicotine. Clin. Pharmacol. Ther. 41:474-479.

Leeder, S.R.; Corkhill, R.T.; Irwig, L.M.; Holland, W.W.; Colley, J.R. (1976) Influence of family factors on the incidence of lower respiratory illness during the first year of life. Br. J. Prev. Soc. Med. 30:203-212.

Lehnert, G. (1984) Roundtable discussion from symposium on medical perspectives on passive smoking. Prev. Med. 13:732-733.

Levin (1953) (p. 6-13).

Lewak, N.; van den Berg, B.J.; Beckwith, J.B. (1979) Sudden infant death syndrome risk factors. Clin. Pediatr. (Phila) 18:404-411.

Lewis, H.M.; Haeney, M.; Jeacock, J.; Thomas, H. (1989) Chronic cough in a hospital population: its relationship to atopy and defect in host defence. Arch. Dis. Child. 64:1593-1598.

Lewtas, J.; Claxton, L.; Mumford, J.L. (1987) Human exposure to mutagens from indoor combustion sources. In: Seifert, B.; Esdorn, M.; Fischer, M.; Ruden, H.; Wegner, J., eds. Indoor air '87, Vol. 1, Oraniendruck GmbH, Berlin, pp. 473-477.

Ling, P.I.; Lofroth, G.; Lewtas, J. (1987) Mutagenic determination of passive smoking. Toxicol. Lett. 35:147-151.

Liu, Z.; He, X.; Chapman, R.S. (1991) Smoking and other risk factors for lung cancer in Xuanwei, China. Int. J. Epidemiol. 20:26-31.

Löfroth, G.; Nilsson, L.; Alfeim, I. (1983) Passive smoking and urban air pollution: Salmonella/microsome mutagenicity assay of simultaneously collected indoor and outdoor particulate matter. In: Waters, M.D.; Sandhu, S.S.; Lewtas, J.; Claxton, L.; Chernoff, N.; Nesnow, S., eds. Short-term bioassays in the analysis of complex environmental mixtures, Vol. III. New York: Plenum, pp. 515-525.

Löfroth, G.; Ling, P.I.; Agurell, E. (1988) Public exposure to environmental tobacco smoke. Mutat. Res. 202:103-110.

Löfroth, G.; Burtin, R.; Forehand, L.; Hammond, K.; Selia, R.; Zwiedinger, E.; Lewtas, J. (1989) Characterization of genotoxic components of environmental tobacco smoke. Environ. Sci. Technol. 23:610-614.

Lossing, E.H.; Best, E.W.R.; McGregor, J.T.; Josie, G.H.; Walker, C.B.; Delaquis, F.M.; Baker, P.M.; McKenzie, A.C. (1966) A Canadian study of smoking and health. Ottawa, Canada: Department of National Health and Welfare.

Lubin, J.H.; Blot, W.J.; Berrino, F.; Flamant, R.; Gillis, C.R.; Kunze, M.; Schmahl, D.; Visco, G. (1984) Modifying risk of developing lung cancer by changing habits of cigarette smoking. Br. Med. J. 288:1953-1956.

MacDonald, E.J. (1981) [Letter] Br. Med. J. 283:915-916.

Machlin, S.R.; Kleinman, J.C.; Madans, J.H. (1989) Validity of mortality analysis based on retrospective smoking information. Stat. Med. 8:997-1009.

Maclure, M.; Katz, R.B.-A.; Bryant, M.S.; Skipper, P.L.; Tannenbaum, S.R. (1989) Elevated blood levels of carcinogens in passive smokers. Am. J. Public Health 79:1381-1384.

Magnusson, C.G.M. (1986) Maternal smoking influences cord serum IgE and IgD levels and increases the risk for subsequent infant allergy. J. Allergy Clin. Immunol. 78:898-904.

Makin, J.; Fried, P.A.; Watkinson, B. (1991) A comparison of active and passive smoking during pregnancy: long-term effects. Neurotoxicol. Teratol. 13:5-12.

Malloy, M.H.; Kleinman, J.C.; Land, G.H.; Schramm, W.F. (1988) The association of maternal smoking with age and cause of infant death. Am. J. Epidemiol. 128:46-55.

Mantel, N. (1963) Chi-square tests with one degree of freedom: extensions of the Mantel-Haenszel procedure. J. Am. Stat. Assoc. 58:690-700.

Mantel, N.; Haenszel, W. (1959) Statistical aspects of the analysis of data from retrospective studies of disease. J. Natl. Cancer Inst. 22:719-748.

Maran, A.G.D.; Wilson, J.A. (1986) Glue ear and speech development. Br. Med. J. 293:713-714.

Marbury, M.C.; Hammond, S.K.; Haley, N.J. (1990) Assessing exposure to environmental tobacco smoke in epidemiological studies of acute health effects. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2. Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 189-194.

Marchand, L.L.; Wilkens, L.R.; Hankin, J.H.; Haley, N.J. (1991) Dietary patterns of female nonsmokers with and without exposure to environmental tobacco smoke. Cancer Causes and Control 2:11-16.

Martin, T.R.; Bracken, M.B. (1986) Association of low birth weight with passive smoke exposure in pregnancy. Am. J. Epidemiol. 124:633-642.

Martinez, F.D.; Morgan, W.J.; Wright, A.L.; Holberg, C.J.; Taussig, L.M. (1988a) Diminished lung function as a predisposing factor for wheezing lower respiratory tract illness in infants. N. Engl. J. Med. 319:1112-1117.

Martinez, F.D.; Antognoni, G.; Macri, F.; Bonci, E.; Midulla, F.; De Castro, G.; Ronchetti, R. (1988b) Parental smoking enhances bronchial responsiveness in nine-year-old children. Am. Rev. Respir. Dis. 138:518-523.

Martinez, F.D.; Morgan, W.J.; Wright, A.L.; Holberg, C.; Taussig L.M. (1991a) Initial airway function is a risk factor for recurrent wheezing respiratory illnesses during the first three years of life. Am. Rev. Respir. Dis. 143:312-316.

Martinez, F.D.; Cline, M.; Burrows, B. (1991b) Increased incidence of asthma in children of smoking mothers. Pediatrics: in press.

Masi, M.A.; Hanley, J.A.; Ernst, P.; Becklake, M.R. (1988) Environmental exposure to tobacco smoke and lung function in young adults. Am. Rev. Respir. Dis. 138:296-299.

Mattson, M.E.; Boyd, G.; Byar, D.; Brown, C.; Callahan, J.F.; Cullen, J.W.; Grenblatt, J.; Haley; Hammond, N.; J.F.; Lewtas, J.; Reeves, W. (1989) Passive smoking on commercial airline flights. JAMA 261:867-872.

McConnochie, K.M.; Roghmann, K.J. (1986a) Parental smoking, presence of older sibling, and family history of asthma increase risk of bronchiolitis. Am. J. Dis. Child. 140:806-812.

McConnochie, K.M.; Roghmann, K.J. (1986b) Breast feeding and maternal smoking as predictors of wheezing in children age 6 to 10 years. Pediatr. Pulmonol. 2:260-268.

Mertsola, J.; Ruuskanen, O.; Vanto, T.; Koivikko, A.; Halonen, P. (1991) Recurrent wheezy bronchitis and viral respiratory infections. Arch. Dis. Child. 66:124-129.

Meyers, D.A.; Beaty, T.H.; Freidhoff, L.R.; Marsh, D.G. (1987) Inheritance of total serum IgE (basal level) in man. Am. J. Hum. Genet. 41:51-62.

Miesner, E.A.; Rudnick, S.N.; Hu, F.; Spengler, J.D.; Preller, L.; Ozkaynak, H.; Nelson, W. (1989) Particule and nicotine sampling in public facilities and offices. J. Air Pollut. Control Assoc. 39:1577-1582.

Miller, G.H. (1984) Cancer, passive smoking and nonemployed and employed wives. West. J. Med. 140(4):632-635.

Mitchell, E.A.; Scragg, R.; Stewart, A.W.; et al. (1991) Results from the first year of the New Zealand cot death study. N.Z. Med. J. 104:71-6.

Moolgavkar, S.H.; Dewanji, A.; Luebeck, G. (1989) Cigarette smoking and lung cancer: reanalysis of the British doctors' data. J. Am. Cancer Inst. 81(6):415-420.

Moschandreas, D.J. (1981) Exposure to pollutants and daily time budgets of people. Bull. N.Y. Acad. Med. 57:845-859.

Mumford, J.L.; Lewtas, J.; Burton, R.M.; Henderson, F.W.; Forehand, L.; Allison, J.C.; Hammond, S.K. (1989) Assessing environmental tobacco smoke exposure of preschool

children in homes by monitoring air particles, mutagenicity, and nicotine. In: Measurement of toxic and related air pollutants, Environmental Protection Agency/Air and Waste Management Association international symposium. Pittsburgh, PA: Air and Waste Management Association, pp. 606-610.

Muramatsu, M.; Umemura, S.; Okada, T.; Tomita, H. (1984) Estimation of personal exposure to tobacco smoke with a newly developed nicotine personal monitor. Environ. Res. 35:218-227.

Murray, A.B.; Morrison, B.J. (1986) The effect of cigarette smoke from the mother on bronchial responsiveness and severity of symptoms in children with asthma. J. Allergy Clin. Immunol. 77:575-581.

Murray, A.B.; Morrison, B.J. (1988) Passive smoking and the seasonal difference of severity of asthma in children. Chest 94:701-708.

Murray, A.B.; Morrison, B.J. (1989) Passive smoking by asthmatics: its greater effect on boys than on girls and on older than on younger children. Pediatrics 84:451-459.

Naeye, R.L.; Ladis, B.; Drage, J.S. (1976) Sudden infant death syndrome. A prospective study. Am. J. Dis. Child. 130:1207-1210.

Nagda, N.; Fortmann, R.; Koontz, M.; Konheim, A. (1990) Investigation of cabin air-quality aboard commercial airlines. In: indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air. Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 245-250.

National Institute for Occupational Safety and Health. (1991) Environmental tobacco smoke in the workplace: lung cancer and other health effects. Current Intelligence Bulletin 54. U.S. Department of Health and Human Services, National Institute for Occupational Safety and Health.

National Research Council. (1986) Environmental tobacco smoke: measuring exposures and assessing health effects. Washington, DC: National Academy Press.

National Research Council. (1987) Indoor pollutants. Washington, DC: National Academy Press, p. 537.

Neal, A.D.; Wadden, R.A.; Rosenberg, S. (1978) Evaluation of indoor particulate concentrations for an urban hospital. Am. Ind. Hyg. Assoc. J. 29:578-582.

Neddenriep, D.; Martinez, F.D.; Morgan, W.J. (1990) Increased specific lung compliance in newborns whose mothers smoked during pregnancy. Am. Rev. Respir. Dis. 141:A282.

Nelson, P.A.; Qvant, F.R.; Sem, G.F. (1982) Experimental measurements of aerosol concentrations in offices. Environ. Int. 8:223-227.

Neuspiel, D.R.; Rush, D.; Butler, N.; Golding, J.; Bijur, P.E.; Kurzon, M. (1989) Parental smoking and post-infancy wheezing in children: a prospective cohort study. Am. J. Public Health 79:168-171.

NIOSH. *See* National Institute for Occupational Safety and Health.

Nitschke, I.A.; Clarke, W.A.; Clarkin, M.E.; Traynmor, G.W.; Wadach, J.B. (1985) Indoor air quality infiltration and ventilation in residential buildings. NYSERDA #85-10. Albany, NY: New York State Energy Research and Development Authority.

NRC. *See* National Research Council.

O'Connell, E.J.; Logan, G.B. (1974) Parental smoking in childhood asthma. Annals of Allergy 32:142-145.

O'Connor, G.T.; Weiss, S.T.; Tager, I.B.; Speizer, F.E. (1987) The effect of passive smoking on pulmonary function and non-specific bronchial responsiveness in a population based sample of children and young adults. Am. Rev. Respir. Dis. 135:800-804.

O'Connor, G.T.; Sparrow, D.; Weiss, S.T. (1989) The role of allergy and nonspecific airway hyperresponsiveness in the pathogenesis of chronic obstructive pulmonary disease. Am. Rev. Respir. Dis. 140:225-252.

Ogden, M.W.; Nystrom, C.W.; Oldaker, G.B., III; Conrad, F.W., Jr. (1989) Evaluation of a personal passive sampling device for determining exposure to nicotine in environmental tobacco smoke. In: Measurement of toxic and related air pollutants. Pittsburgh, PA: Air Pollution Control Association, pp. 552-558.

Ogston, S.A.; Florey, C. du V.; Walker, C.M. (1987) Association of infant alimentary and respiratory illness with parental smoking and other environmental factors. J. Epidemiol. Community Health 41:21-25.

Oldaker, G.B., III; Conrad, F.W., Jr. (1987) Estimation of the effect of environmental tobacco smoke (ETS) on air quality within aircraft cabins of commercial aircraft. Environ. Sci. Technol. 21:994-999.

Oldaker, G.B.; Ogden, M.W.; Maiolo, K.C.; Conner, J.M.; Conrad, F.W.; DeLuca, P.O. (1990) Results from surveys of environmental tobacco smoke in restaurants in Winston-Salem, North Carolina. In: Indoor air '90: proceedings of the 5th international conference on indoor air quality and climate, July 29-August 3. Vol. 2: Characteristics of indoor air, Ottawa, Ontario, Canada: Canada Mortgage and Housing Corporation, pp. 281-285.

Oldigs, M.; Jrres, R.; Magnussen, H. (1991) Acute effects of passive smoking on lung function and airway responsiveness in asthmatic children. Pediatr. Pulmonol. 10:123-131.

Ong, T.M.; Stewart, J.; Whong, W.Z. (1984) A simple in situ mutagenicity test for detection of mutagenic air pollutants. Mutat. Res. 139:177-181.

Park, J.K.; Kim, I.S. (1986) Effect of family smoking on acute respiratory disease in children. Yonsei Med. J. 27:261-270.

Parker, G.B.; Wilfert, G.L.; Dennis, G.W. (1984) Indoor air quality and infiltration in multifamily naval housing. Annual PNWIS/APCA meeting, Portland, OR, Nov. 12-14, pp. 1-14.

Pattishall, E.N.; Strope, G.L.; Etzel, R.A.; Helms, R.W.; Haley, N.J.; Denny, F.W. (1985) Serum cotinine as a measure of tobacco smoke exposure in children. Am. J. Dis. Child. 139:1101-1104.

Pedreira, F.A.; Guandolo, V.L.; Feroli, E.J.; Mella, G.W.; Weiss, I.P. (1985) Involuntary smoking and incidence of respiratory illness during the first year of life. Pediatrics 75:594-597.

Perera, F.R.; Santella, R.M.; Brenner, D.; Poirier, M.C.; Munshi, A.A.; Fischman, H.K.; Van Ryzin, J. (1987) DNA adducts, protein adducts, and sister chromatid exchange in cigarette smokers and nonsmokers. J. Natl. Cancer Inst. 79:449-456.

Pershagen, G.; Hrubec, Z.; Svensson, C. (1987) Passive smoking and lung cancer in Swedish women. Am. J. Epidemiol. 125(1):17-24.

Peto, R.; Doll, R. (1984) Keynote address: the control of lung cancer. In: Mizell, M.; Correa, P., eds. Lung cancer: causes and prevention. New York: Verlag Chemie International, pp. 1-19.

Phillips, R.L.; Garfinkel, L.; Kuzma, J.W.; et al. (1980a) Mortality among California Seventh-Day Adventists for selected cancer sites. J. Natl. Cancer Inst. 65:1097-1107.

Phillips, R.L.; Kuzma, J.W.; Beeson, W.L.; et al. (1980b) Influence of selection versus lifestyle on risk of fatal cancer and cardiovascular disease among Seventh-Day Adventists. Am. J. Epidemiol. 112:296-314.

Pierce, J.P.; Dwyer, T.; et al. (1987) Cotinine validation of self-reported smoking in commercially run community surveys. J. Chronic. Dis. 40:689-695.

Pierce, J.P.; Fiore, M.C.; Novotny, T.E.; Hatziandreu, E.J.; Davis, R.M. (1989) Trends in cigarette smoking in the United States. Projections to the year 2000. JAMA 261:61-65.

Pimm, P.E.; Silverman, F.; Shepard, R.J. (1978) Physiological effects of acute passive exposure to cigarette smoke. Arch. Environ. Health 33:201-213.

Pojer (1984).

Pukander, J.; Luotonen, J.; Timonen, J.; Karma, P. (1985) Risk factors affecting the occurrence of acute otitis media among 2-3-year old urban children. Acta Otolaryngol. 100:260-265.

Pullan, C.R.; Hey, E.N. (1982) Wheezing, asthma, and pulmonary dysfunction 10 years after infection with respiratory sycytial virus in infancy. Br. Med. J. 284:1665-1669.

Putnam, D.L.; David, R.M.; Melhorn, J.M.; Dansie, D.R.; Stone, C.J.; Henry, C.J. (1985) Dose-responsive increase in sister-chromatid exchanges in bone-marrow cells of mice exposed nose-only to whole cigarette smoke. Mutat. Res. 156:181-186.

Quant, F.R.; Nelson, P.A.; Sem, G.J. (1982) Experimental measurements of aerosol concentrations in offices. Environ. Int. 8(1-6):249-258.

Rantakallio, P. (1978) Relationship of maternal smoking to morbidity and mortality of the child up to the age of five. Acta Paediatr. Scand. 67:621-631.

Reed, B.D.; Lutz, L.J. (1988) Household smoking exposure—association with middle ear effusions. Fam. Med. 20:426-430.

Remmer, H. (1987) Passively inhaled tobacco smoke: a challenge to toxicology and preventive medicine. Arch. Toxicol. 61:89-104.

Repace, J.L. (1987) Indoor concentrations of environmental tobacco smoke: models dealing with effects of ventilation and room size. In: O'Neill, I.K.; Brunnemann, K.D.; Dodet, B.; Hoffmann, D., eds. Environmental carcinogens—selected methods of analysis, v. 9, passive smoking. Chapter 3, IARC Monographs No. 81. Lyon, France: International Agency for Research on Cancer.

Repace, J.L. (1989) Workplace restrictions on passive smoking: justification on the basis of cancer risk (in press).

Repace, J.L.; Lowrey, A.H. (1980) Indoor air pollution, tobacco smoke and public health. Science 208:464-472.

Repace, J.L.; Lowrey, A.H. (1982) Tobacco smoke, ventilation and indoor air quality. Am. Soc. Heat Refrig. Air Cond. Eng. Trans. 88:894-914.

Repace, J.L.; Lowrey, A.H. (1985) A quantitative estimate of nonsmokers' lung cancer risk from passive smoking. Environ. Intl. 11:3-22.

Repace, J.L.; Lowrey, A.H. (1990) Risk assessment methodologies in passive smoking. Risk Anal. 10(1):27-37.

Riboli, E.; Preston-Martin, S.; Saracci, R.; Haley, N.J.; et al. (1990) Exposure of nonsmoking women to environmental tobacco smoke: a 10-country collaborative study. Cancer Causes and Control 1:243-252.

Rickert, W.S.; Robinson, J.C.; Collinshaw, N.E. (1984) Yields of tar, nicotine and carbon monoxide in the sidestream smoke from 15 brands of Canadian cigarettes. Am. J. Public Health 74:228-231.

Rijcken, B.; Schouten, J.P.; Weiss, S.T.; Speizer, F.E.; Van der Lende, R. (1987) The relationship of nonspecific bronchial responsiveness to respiratory symptoms in a random population sample. Am. Rev. Respir. Dis. 136:62-68.

Rimington, J. (1981) The effect of filters on the incidence of lung cancer in cigarette smokers. Environ. Res. 24:162-166.

Robins, J.M.; Blebins, D.; Schneiderman, M (1989) The effective number of cigarettes inhaled daily by passive smokers: are epidemiologic and dosimetric estimates consistent? J. Haz. Mat. 21:215-238.

Rogot, E.; Murray, J.L. (1980) Smoking and causes of death among U.S. veterans: 16 years of observation. Public Health Rep. 95:213-222.

Ronchetti, R.; Macri, F.; Ciofetta, G.; et al. (1990) Increased serum immunoglobulin E and increased prevalence of eosinophilia in 9-year-old children of smoking parents. J. Allergy Clin. Immunol. 86:400-407.

Rothman, K.J. (1986) Modern epidemiology. Boston: Little, Brown and Co.

Russell, M.A.H.; Feyerabend, C. (1975) Blood and urinary nicotine in nonsmokers. Lancet 1:179-181.

Russell, M.A.H.; Jarvis, M.J.; West, R.J. (1986) Use of urinary nicotine concentrations to estimate exposure and mortality from passive smoking in non-smokers. Br. J. Addict. 81:275-281.

Rylander, E.; Eriksson, M.; Freyschuss, U. (1988) Risk factors for occasional and recurrent wheezing after RSV infection in infancy. Acta Pediatr. Scand. 77:711-715.

Said, G.; Zalokar, J.; Lellouch, J.; Patois, E. (1978) Parental smoking related to adenoidectomy and tonsillectomy in children. J. Epidemiol. Community Health 32:97-101.

Samet, J.M.; Tager, I.B.; Speizer, F.E. (1983) The relationship between respiratory illness in childhood and chronic air-flow obstruction in adulthood. Am. Rev. Respir. Dis. 127:508-523.

Sandler, D.P.; Everson, R.B.; Wilcox, A.J. (1985) Passive smoking in adulthood and cancer risk. Am. J. Epidemiol. 121(1):37-48.

Saracci, R. (1989) Passive smoking and cancer risk. IARC report of panel of experts. Prepared at the request of the European School of Oncology through the Europe Against Cancer program of the European Economic Community.

Saracci, R.; Riboli, E. (1989) Passive smoking and lung cancer: current evidence and ongoing studies at the International Agency for Research on Cancer. Mutat. Res. 222:117-127.

Schelesselman, J.J. (1978) Assessing effects of confounding variables. Am. J. Epidemiol. 108:3-8.

Schelesselman, J.J. (1982) Case-control studies: design, conduct, analysis. New York: Oxford University Press.

Schenker, M.B.; Samet, J.M.; Speizer, E.F. (1983) Risk factors for childhood respiratory disease. The effect of host factors and home environment exposures. Am. Rev. Respir. Dis. 128:1038-1043.

Schenker, M.B.; Samuels, S.J.; Kado, N.Y.; Hammond, S.K.; Smith, T.J.; Woskie, S.R. (1990) Markers of exposure to diesel exhaust. Research Publication Number 33. Cambridge, MA: Health Effects Institute.

Schilling, R.S.F.; Letai, A.D.; Hui, S.L.; Beck, G.J.; Schoenberg, J.B.; Bouhuys, A. (1977) Lung function, respiratory disease, and smoking in families. Am. J. Epidemiol. 106:274-283.

Schwartz, J.; Zeger, S. (1990) Passive smoking, air pollution, and acute respiratory symptoms in a diary of student nurses. Am. Rev. Respir. Dis. 141:62-67.

Seely, J.E.; Zuskin, E.; Bouhuys, A. (1971) Cigarette smoking: objective evidence for lung damage in teen-agers. Science 172:741-743.

Seigel, D.G.; Greenhouse, S.W. (1973) Validity in estimating relative risk in case-control studies. J. Chronic Dis. 26:219-226.

Sexton, K.; Spengler, J.D.; Treitman, R.D. (1984) Personal exposure to respirable particulates: a case-study in Waterbury, Vermont. Atmos. Environ. 18:1385-1398.

Shephard, R.J. (1992) Respiratory irritation from ETS. Arch. Env. Health 47:(2):123-130.

Shephard, R.J.; Collis, R.; Silverman, F. (1979) "Passive" exposure of asthmatic subjects to cigarette smoke. Environ. Res. 20:392-402.

Sherman, C.B.; Tosteson, T.D.; Tager, I.B.; Speizer, F.E.; Weiss, S.T. (1990) Early childhood predictors of asthma. Am. J. Epidemiol. 132:83-95.

Sherrill, D.; Holberg, C.J.; Lebowitz, M.D. (1990) Differential rates of lung growth as measured longitudinally by pulmonary function in children and adolescents. Pediatr. Pulmonol. 8:145-154.

Shimizu, H.; Morishita, M.; Mizuno, K.; Masuda, T.; Ogura, Y.; Santo, M.; Nishimura, M.; Kunishima, K.; Karasawa, K.; Nishiwaki, K.; Yamamoto, M.; Hisamichi, S.; Tominaga, S. (1988) A case-control study of lung cancer in nonsmoking women. Tohoku J. Exp. Med. 154:389-397.

Shultz, T.M., Novotny, T.E.; Rice, D.P. (1991) Quantifying the disease impact of cigarette smoking with SAMMEC II Software. Public Health Reports 106(3)326-333.

Sidney, S.; Caan, B.; Friedman, G. (1989) Dietary intake of carotene in nonsmokers with and without passive smoke at home. Am J Epidimiol 129:1305-9.

Sims, D.G.; Downham, M.A.P.S.; Gardner, P.S.; Webb, J.K.G.; Weightman, D. (1978) Study of 8-year-old children with a history of respiratory syncytial virus bronchiolitis in infancy. Br. Med. J. 1:11-14.

Sobue, T.; Suzuki, R.; Nakayama, N.; Inubuse, C.; Matsuda, M.; Doi, O.; Mori, T.; Furuse, K.; Fukuoka, M.; Yasumitsu, T.; Kuwabara, O.; Ichigaya, M.; Kurata, M.; Nakahara, K.; Endo, S.; Hattori, S. (1990) Passive smoking among nonsmoking women and the relationship between indoor air pollution and lung cancer incidence—results of a multicenter case controlled study. Gan to Rinsho 36(3):329-333.

Somerville, S.M.; Rona, R.J.; Chinn, S. (1988) Passive smoking and respiratory conditions in primary school children. J. Epidemiol. Community Health 42:105-110.

Sparrow, D.; O'Connor, G.; Colton, T.; Barry, C.L.; Weiss, S.T. (1987) The relationship of nonspecific bronchial responsiveness to the occurrence of respiratory symptoms and decreased levels of pulmonary function. The normative aging study. Am. Rev. Respir. Dis. 135:1255-1260.

Speizer, F.E.; Ferris, B., Jr.; Bishop, Y.M.; Spengler, J. (1980) Respiratory disease rates and pulmonary function in children associated with NO exposure. Am. Rev. Respir. Dis. 121:3-10.

Spengler, J.D.; Dockery, D.W.; Turner, W.A.; Wolfson, J.M.; Ferris, B.G. (1981) Long-term measurements of respirable sulphates and particles inside and outside homes. Atmos. Environ. 15:23-30.

Spengler, J.D.; Treitman, R.D.; Tosteson, T.D.; Mage, D.T.; Soczek, M.L. (1985) Personal exposures to respirable particulates and implications for air pollution epidemiology. Environ. Sci. Technol. 19:700-707.

Spitzer, W.O.; Lawrence, V.; Dales, R.; Hill, G.; Archer, M.C.; Clark, P.; Abenhaim, L.; Hardy, J.; Sampalis, J.; Pinfold, S.P.; Morgan, P.P. (1990) Links between passive smoking and disease: a best evidence synthesis. A report of the working group on passive smoking. Clin. Invest. Med. 13:17-42.

Stahlman, M.T.; Gray, M.E. (1984) Ontogeny of neuroendocrine cells in human fetal lung. I. An electron microscopic study. Lab. Invest. 51:449-463.

Stanton, M.F.; Miller, E.; Wrench, C.; Blackwell, R. (1972) Experimental induction of epidermoid carcinoma in the lungs of rats by cigarette smoke condensate. J. Natl. Cancer Inst. 49:867-877.

Steele, R.; Langworth, J.T. (1966) The relationship of antenatal and postnatal factors to sudden unexpected death in infancy. Can. Med. Assoc. J. 94:1165-1171.

Steenland, K. (1992) Passive smoking and the risk of heart disease. JAMA 267:94-99.

Stellman, S. D.; Garfinkel, L. (1986) Smoking habits and tar levels in a new American Cancer Society prospective study of 1.2 million men and women. J. Natl. Cancer Inst. 76(6):1057-1063.

Sterling, T.D.; Sterling, E.M. (1983) Investigations on the effect of regulating smoking on levels of indoor pollution and on the preception of health on comfort of office workers. Eur. J. Respir. Dis. 65 (Suppl. 133):17-32.

Stockwell (1990) (p. B-7).

Stockwell, H.G.; Candelora, E.C.; Armstrong, A.W.; Pinkham, P.A. (1991) Environmental tobacco smoke and lung cancer in never smoking women. Presented at the annual meeting abstract forum: Society for Epidemiologic Research, June 12-14, 1991, Buffalo, New York.

Strachan, D.P. (1988) Damp housing and childhood asthma: validation of reporting of symptoms. Br. Med. J. 297:1223-6.

Strachan, D.P.; Jarvis, M.J.; Feyerabend, C. (1990) The relationship of salivary cotinine to respiratory symptoms, spirometry, and exercise-induced bronchospasm in seven-year-old children. Am. Rev. Respir. Dis. 142:147-151.

Strachan, D.P.; Jarvis, M.J.; Feyerabend, C. (1989) Passive smoking, salivary cotinine concentrations, and middle ear effusion in 7 year old children. Br. Med. J. 298:1549-1552.

Sutton (1980) (p. B-14).

Svendsen, K.H.; Kuller, L.H.; Martin, M.J.; Ockene, J.K. (1987) Effects of passive smoking in the multiple risk intervention trial. Am. J. Epidemiol. 126:783-795.

Svensson, D. (1988) Lung cancer etiology in women. [Dissertation] Karolinska Institute, Stockholm, Sweden.

Svensson, C.; Pershagen, G.; Klominek, J. (1988) Smoking and passive smoking in relation to lung cancer in women. Department of Epidemiology, National Institute of Environmental Medicine, Stockholm, Sweden.

Svensson, C.; Pershagen, G.; Klominek, J. (1989) Smoking and passive smoking in relation to lung cancer in women. Acta Oncol. 28:623-629.

Tager, I.B.; Segal, M.R.; Munoz, A.; Weiss, S.T.; Speizer, F.E. (1987) The effect of maternal smoking on the pulmonary function of children and adolescents. Analysis of data from two populations. Am. Rev. Respir. Dis. 136:1366-1370.

Tager, I.B.; Weiss, S.T.; Munoz, A.; Rosner, B.; Speizer, F.E. (1983) Longitudinal study of the effects of maternal smoking on pulmonary function in children. N. Engl. J. Med. 309:699-703.

Tager, I.B.; Weiss, S.T.; Rosner, B.; Speizer, F.E. (1979) Effect of parental cigarette smoking on the pulmonary function of children. Am. J. Epidemiol. 110:15-26.

Tainio, V.M.; Savilahti, E.; Salmenpera, L.; Arjomaa, P.; Siimes, M.A.; Perheentupa, J. (1988) Risk factors for infantile recurrent otitis media: atopy but not type of feeding. Pediatr. Res. 23:509-12.

Takasaka, T. (1990) Incidence, prevalence, and natural history of otitis media in different geographic areas and populations. Ann. Otol. Rhinol. Laryngol. 99:13-14.

Tashkin, D.P.; Clark, V.A.; Simmons, M.; Reems, C.; Coulson, A.H.; Bourque, L.B.; Sayre, J.W.; Detels, R.; Rokaw, S. (1984) The UCLA population studies of chronic obstructive respiratory disease. VII. Relationship between parental smoking and children's lung function. Am. Rev. Respir. Dis. 129:891-897.

Taylor, R.G.; Gross, E.; Joyce, H.; Holland, F.; Pride, N.B. (1985) Smoking, allergy, and the differential white blood cell count. Thorax 40:17-22.

Teele, D.W.; Klein, J.O.; Rosner, B. (1989) Epidemiology of otitis media during the first seven years of life in children in greater Boston: a prospective, cohort study. J. Infect. Dis. 160: 83-94.

Toyoshima, K.; Hayashida, M.; Yasunami, J.; Takamatsu, I.; Niwa, H.; Muraoka, T. (1987) Factors influencing the prognosis of wheezy infants. J. Asthma. 24:267-270.

Trichopoulos, D.; Kalandidi, A.; Sparros, L. (1983) Lung cancer and passive smoking: conclusion of Greek study. [Letter] Lancet 667-668.

Trichopoulos, D.; Kalandidi, A.; Sparros, L.; MacMahon, B. (1981) Lung cancer and passive smoking. Int. J. Cancer 27:1-4.

Trichopoulos, D. (1988) Passive smoking and lung cancer. Scand. J. Soc. Med. 16:75-79.

Tsimoyianis, G.V.; Jacobson, M.S.; Feldman, J.G.; Antonio-Santiago, M.T.; Clutario, B.C.; Nussbaum, M.; Shenker, I.R. (1987) Reduction in pulmonary function and increased frequency of cough associated with passive smoking in teenage athletes. Pediatrics 80:32-36.

Uberla, K.; Ahlborn, W. (1987) Passive smoking and lung cancer; a reanalysis of Hirayama's data. In: Proceedings of international conference on indoor air quality. Tokyo: Council for Environment and Health, p. 41.

U.S. Bureau of the Census (1990). Statistical abstract of the United States, 1990.

U.S. Department of Health and Human Services. (1982) The health consequences of smoking: cancer. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service.

U.S. Department of Health and Human Services. (1983) The health consequences of smoking: cardiovascular disease. A report of the Surgeon General. DHHS Pub. No. (PHS) 84-50204. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

U.S. Department of Health and Human Services. (1984) The health consequences of smoking: chronic obstructive lung disease. A report of the Surgeon General. DHHS Pub. No. (PHS) 84-50205. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

U.S. Department of Health and Human Services. (1986) The health consequences of involuntary smoking. A report of the Surgeon General. DHHS Pub. No. (PHS) 87-8398. U.S. Department of Health and Human Services, Public Health Service, Office of the Assistant Secretary for Health, Office of Smoking and Health.

U.S. Department of Health and Human Services. (1989) Reducing the health consequences of smoking: 25 years of progress. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service.

U.S. Department of Health and Human Services. (1990) The health benefits of smoking cessation. A report of the Surgeon General. U.S. Department of Health and Human Services, Public Health Service.

U.S. Department of Health and Human Services. (1990b) Vital and health statistics: current estimates from the national health interview survey, 1989. p.129.

U.S. Department of Health, Education, and Welfare. (1964) Smoking and health. Report of the Advisory Committee to the Surgeon General of the Public Health Service. PHS Pub. No. 1103.

U.S. Department of Health, Education, and Welfare. (1977) Nicotine. NIOSH manual of analytical methods, Vol. 3, 2nd Ed., Publication No. 77-157-C.

U.S. DHEW. *See* U.S. Department of Health, Education, and Welfare.

U.S. DHHS. *See* U.S. Department of Health and Human Services.

U.S. Department of Transportation. (1971) Health aspects of smoking in transport aircraft. Washington, DC: U.S. Department of Transportation, National Technical Information Service.

U.S. Environmental Protection Agency. (1986a) Guidelines for carcinogen risk assessment. Federal Register 51:33992-34003.

U.S. Environmental Protection Agency. (1986b) Guidelines for the health risk assessment of chemical mixtures. Federal Register 51:34014-34025.

U.S. Environmental Protection Agency. (1989) Workshop report on EPA guidelines for carcinogen risk assessment: Use of human evidence, September 1989.

U.S. Environmental Protection Agency (EPA). (1990) Health effects of passive smoking: assessment of lung cancer in adults and respiratory disorders in children. External Review Draft. EPA/600/6-90/006A.

U.S. EPA. *See* U.S. Environmental Protection Agency.

Varela, L.R. (1987) Assessment of the association between passive smoking and lung cancer. [doctoral dissertation]. New Haven, CT: Yale University.

Vaughan, W.M.; Hammond, S.K. (1990) Impact of designated smoking area. Policy on nicotine vapor and particle concentrations in a modern office building. J. Air Waste Management Assoc. 40:1012-1017.

Vedal, R.E.; Schenker, M.B.; Samet, J.M.; Speizer, F.E. (1984) Risk factors for childhood respiratory disease. Am. Rev. Respir. Dis. 130:187-192.

Vidic, B.; Ujevic, N.; Shabahang, M.M.; Van de Zande, F. (1989) Differentiation of interstitial cells and stromal proteins in the secondary septum of early postnatal rat: effect of maternal chronic exposure to whole cigarette smoke. Anat. Rec. 165:165-173.

Vincent, T.N.; Satterfield, J.V.; Ackerman, L.V. (1965) Carcinoma of the lung in women. Cancer 18:559-570.

Vincent, R.G.; Pickren, J.W.; Lane, W.W.; Bross, I.; Takita, H.; Houten, L.; Gutierrez, A.C.; Rzepka, T. (1977) The changing histopathology of lung cancer: a review of 1682 cases. Cancer 39:1647-1655.

Vutuc, C. (1984) Quantitative aspects of passive smoking and lung cancer. Prev. Med. 13:698-704.

Wald, N.J.; Boreham, J.; Bailey, A.; et al. (1984) Urinary cotinine as a marker of breathing other people's tobacco smoke. Lancet 1:230-231.

Wald, N.J.; Ritchie, C. (1984) Validation of studies on lung cancer in nonsmokers married to smokers. Lancet 1:1067.

Wald, N.J.; Nanchahal, K.; Thompson, S.G.; Cuckle, H.S. (1986) Does breathing other people's tobacco smoke cause lung cancer? Br. J. Med. 293:1217-1222.

Wall, M.; Johnson, J.; Jacob, P.; Benowitz, N. (1988) Cotinine in the serum, salivia, and urine of nonsmokers, passive smokers, and active smokers. Am. J. Public Health 78:699-701.

Wang, N.S.; Chen, M.F.; Schraufnagel, D.E. (1984) The cumulative scanning electron microscopic changes in baby mouse lungs following prenatal and postnatal exposures to nicotine. J Pathol. 144:89-100.

Ware, J.H.; Dockery, D.W.; Spiro, A., III.; Speizer, F.E.; Ferris, B.G., Jr. (1984) Passive smoking, gas cooking, and respiratory health of children living in six cities. Am. Rev. Respir. Dis. 129:366-374.

Weber A.; Fischer T.; Grandjean, A. (1979) Passive smoking in experimental and field conditions. Environ. Res. 20:205-216.

Weir, J.M.; Dunn, J.E., Jr. (1970) Smoking and mortality: a prospective study. Cancer 25:105-112.

Weiss, W.; Boucot, K.R.; Seidman, H.; Carnahan, W.J. (1972) Risk of lung cancer according to histologic type and cigarette dosage. JAMA 222:799-801.

Weiss, S.T.; Tager, I.B.; Speizer, F.E.; Rosner, B. (1980) Persistent wheeze: its relation to respiratory illness, cigarette smoking, and level of pulmonary function in a population sample of children. Am. Rev. Respir. Dis. 122:697-707.

Weiss, S.T.; Tager, I.B.; Munoz, A.; Speizer, F.E. (1985) The relationship of respiratory infections in early childhood to the occurrence of increased levels of bronchial responsiveness and atopy. Am. Rev. Respir. Dis. 131:573-578.

Weitzman, M.; Gortmaker, S.; Klein Walker, D.; Sobol, A. (1990) Maternal smoking and childhood asthma. Pediatrics 85:505-11.

Wells, A.J. (1988) An estimate of adult mortality in the United States from passive smoking. Environ. Int. 14:249-265.

Wells, A.J. (1990) Smoker misclassification does not account for observed passive smoking risk for lung cancer. Submission to Indoor Air Quality and Total Human Exposure Committee, Science Advisory Board, U.S. EPA, December 4, 1990.

White, J.R.; Froeb, H.F. (1980) Small airways dysfunction in nonsmokers chronically exposed to tobacco smoke. N. Engl. J. Med. 302:720-723.

Whittemore, A.S. (1988) Effect of cigarette smoking in epidemiological studies of lung cancer. Stat. Med. 7:223-238.

Wigle, D.T.; Collishaw, N.E.; Kirkbride, J.; Mao, Y. (1987) Deaths in Canada from lung cancer due to involuntary smoking. J. Can. Med. Assoc. 136:945-________.

Willatt, D.J. (1986) Children's sore throats related to parental smoking. Clin. Otolaryngol. 11:317-321.

Williamson, D.F.; Serdula, M.K.; Kendrick, J.S.; Binkin, N.C. (1989) Comparing the prevalence of smoking in pregnant and nonpregnant women, 1985 to 1986. JAMA 261:70-74.

Woodward, A.; Douglas, R.M.; Graham, N.M.H.; Miles, H. (1990) Acute respiratory illness in Adelaide children: breast feeding modifies the effect of passive smoking. J. Epidemiol. Community Health 44:224-30.

Woolcock, A.J.; Peat, J.K.; Leeder, S.R.; Blackburn, C.R.B. (1984) The development of lung function in Sydney children: effects of respiratory illnesss and smoking. A ten year study. Eur. J. Resp. Dis. 65(Suppl):1-137.

Woolcock, A.J.; Peat, J.K.; Salome, C.M.; et al. (1987) Prevalence of bronchial hyperresponsivess and asthma in a rural adult population. Thorax 42:361-368.

Woolf, B. (1955) On estimating the relationship between blood group and disease. Ann Human Genet 19:251-253.

Wright, A.L.; Taussig, L.M.; Ray, C.G.; Harrison, H.R.; Holberg, C.J. (1989) The Tucson's children respiratory study. II. Lower respiratory tract illnesses in the first year of life. Am. J. Epidemiol. 129:1232-1246.

Wright, A.L.; Holberg, C.; Martinez, F.D.; Taussig, L.M. (1991) Relationship of parental smoking to wheezing and non-wheezing lower respiratory tract illnesses in infancy. J. Pediatr. 118:207-214.

Wu, A.H.; Henderson, B.E.; Pike, M.D.; Yu, M.C. (1985) Smoking and other risk factors for lung cancer in women. J. Natl. Cancer Inst. 74(4):747-751.

Wu-Williams, A.H.; Samet, J.H. (1990) Environmental tobacco smoke: exposure-response relationships in epidemiologic studies. Risk Anal. 10:1.

Wynder, E.L.; Hoffmann, D. (1967) Tobacco and tobacco smoke: studies in experimental carcinogenesis. New York: Academic Press.

Wynder, E.L.; Stellman, S.D. (1977) Comparative epidemiology of tobacco-related cancers. Cancer Res. 37:4608-4622.

Wynder, E.L.; Gottlieb, S.; Wright, G. (1957) A study of tobacco carcinogenesis. IV. Different tobacco types. Cancer 10:1206-1209.

Wynder, E.L.; Mabuchi, K.; Beattie, E.J., Jr. (1970) The epidemiology of lung cancer: recent trends. JAMA 213:2221-2228.

Xu, Z.Y.; Blot, W.J.; Xiao, H.P.; et al. (seven others) (1989) Smoking, air pollution and the high rates of lung cancer in Shenyand, China. J. Natl. Cancer Inst. 81:1800.

Yarnell, J.W.; St Leger, A.S. (1979) Respiratory illness, maternal smoking habit and lung function in children. Br. J. Dis. Chest 73:230-236.

Young, S.; LeSouef, P.N.; Reese, A.C.; Stick, S.M.; Landau, L.I. (1990) Factors predicting cough and wheeze in the first 6 months of life. Am. Rev. Respir. Dis. 141:A901.

Zahm, S.H.; Cocco, P.; Blair, A. (1991) Tobacco smoking as a risk factor for colon polyps. Am. J. Public Health 81:846-849.

Zetterstrom, O.; Osterman, K.; Machado, L.; Johansson, S.G.O. (1981) Another smoking hazard: raised serum IgE concentration and increased risk of occupational allergy. Br. Med. J. 283:1215-1217.

APPENDIX A

REVIEWS OF EPIDEMIOLOGIC STUDIES ON ETS AND LUNG CANCER

CONTENTS

CONTENTS (continued)

A.1. INTRODUCTION

This appendix contains a review of each epidemiologic study based on the primary references listed in Table 5-1. Descriptions of the four prospective cohort studies are individualized according to the requirements of each study—for example, HIRA(Coh) has a long history of controversy in the literature, so the main arguments are chronicled and discussed as part of the review. Reviews of case-control studies follow a structured format, consisting of three parts: (1) the author's abstract, which summarizes the most salient features and conclusions in the author's opinion; (2) a study description based on the contents of a completed study format designed around principles of good epidemiologic practice and features specific to environmental tobacco smoke (ETS); and (3) a section of comments related to evaluation and interpretation of the study. The author's abstract is, of course, entirely his words; the study description is intended to portray accurately the reference article vis-à-vis items in the study format, so the author's words are used when possible; the comments section is entirely our own assessment of characteristics relevant to study interpretation and utility in this report.

Only an abstract is available for the case-control study by Stockwell et al., referred to as STOC, which has not appeared in print yet. There is insufficient information on the study to include it in the main body of this report. Similarly, only an abstract is available for the second study of Kabat and Wynder, which is included in an addendum following the review of their first study, KABA. The data for many of the studies reviewed have been extracted from a larger, more comprehensive study that includes active smokers. The subjects and their data used for investigation of an association between ETS exposure and lung cancer incidence are referred to as "ETS subjects" and "ETS data," respectively.

A.2. AKIB

A.2.1. Author's Abstract

"A case-control study conducted in Hiroshima and Nagasaki, Japan, revealed a 50% increased risk of lung cancer among nonsmoking women whose husbands smoked. The risks tended to increase with amount smoked by the husband, being highest among women who worked outside the home and whose husbands were heavy smokers, and to decrease with cessation of exposure. The findings provide incentive for further evaluation of the relationship between passive smoking and cancer among nonsmokers."

A.2.2. Study Description

This community-based case-control study was conducted in Hiroshima and Nagasaki, Japan, in 1982. The data collected on passive smoking are part of a larger investigation of lung cancer among atomic bomb survivors, the principal objective of which is to evaluate the interactive roles of cigarette smoking and ionizing radiation. This article reports on married female never-smokers, an unmatched subset of the data from the whole study.

The whole study includes a total of 525 primary lung cancer cases diagnosed between 1971 and 1980. Cases were identified from the Hiroshima and Nagasaki Tumor and Tissue Registries and other records. Controls were selected from among the cohort members without lung cancer, two per case in Hiroshima and three per case in Nagasaki. The controls were individually matched to the cases with respect to year of birth (± 2 years), city of residence (Hiroshima or Nagasaki), sex, biennial medical examinations, and vital status. The majority of cases were deceased; those cases were matched to decedent controls by year of death (± 3 years), in addition to the other criteria. Controls were selected from causes of death other than cancer and chronic respiratory disease. Face-to-face interviews were conducted for 81% (82%) of the eligible cases (controls), but 80% to 85% of the interviews for both cases and controls were actually conducted with the subject's next-of-kin. The mean age of cases at diagnosis is 72.1 years (range 36-94) for males and 70.2 (range 35-95) for females, which is high for lung cancer in Japan. Fifty-seven percent of the cases were pathologically confirmed; the remaining 43% were diagnosed by radiological or clinical findings.

ETS exposure in adulthood was assessed by spousal smoking status, including the average number of cigarettes smoked per day, age the spouse started smoking, and, for those who stopped smoking, the age at cessation. For childhood exposure, a single question was asked regarding whether the subject's mother or father or both smoked when the subject was living at home as a child; responses were obtained for only two-thirds of the subjects. No specific information on exposure to smoking by other household members' smoking or to smoking in the workplace was obtained. ETS exposure data were checked by comparing smoking status with records from RERF surveys in 1964-68 (self-reported by subjects when they were alive). Cases and controls who had never married were excluded. Of the female cases exposed to spousal smoking, 16% had squamous or small cell carcinoma, whereas no unexposed cases had those cell types. No information was provided on location of the carcinomas.

The number of female cases exposed to ETS is 73 out of 94 (number exposed/total) compared with 188 out of 270 female controls (crude odds ratio [OR] is 1.52 [95% C.I. = 0.88-2.63], by our calculations). Application of logistic regression to the whole study that *includes*

active smokers, gives an adjusted odds ratio of 1.5 (90% C.I. = 1.0-2.5), similar to the crude analysis. It is not stated explicitly that matching variables were included in the logistic regression model. Four additional analyses were conducted on the ETS data alone (i.e., without active smokers). The authors stratified exposure by number of cigarettes smoked per day by husband (0, 1-19, 20-29, 30+) and obtained a marginally significant trend ($p = 0.06$). No dose-response gradient was found in the association between the number of years the husband smoked cigarettes and the risk of lung cancer in female never-smokers; the odds ratio *decreases* from lowest to highest exposure level (2.1, 1.5, and 1.3). Stratified analysis according to recency of exposure to husband's smoking (unexposed, exposed but not within the past 10 years, and exposed within the past 10 years) shows a significant upward trend ($p = 0.05$). Further stratification of exposed subjects by occupation found that lung cancer risk tends to increase across occupational categories in the following order: housewife, white collar worker, blue collar worker. The highest odds ratio occurred for women who had blue collar jobs and were married to men who smoked one or more packs of cigarettes per day, but the number involved was small. It is reported that additional analyses on the data indicated that factors for matching in the whole study have little influence, but the details are omitted.

Limited histological information is provided. Among cases exposed to spousal smoking, 16% had squamous or small cell cancer, and 84% had adenocarcinoma or large cell cancer. All of the unexposed cases had adenocarcinoma.

The authors conclude that there may be a moderate excess in lung cancer risk associated with passive smoking. The odds ratio for lung cancer among nonsmoking women tends to increase with amount smoked by their husbands, a trend seen among housewives, as well as among women who work outside the home. There was little association with parental smoking or from passive smoking that had ceased more than 10 years previously.

A.2.3. Comments

The larger study from which the ETS data are taken was primarily intended to investigate the interaction of smoking and ionizing radiation in atomic bomb survivors of Nagasaki and Hiroshima. The information on passive smoking has been collected posthumously in a large percentage of the cases, requiring heavy use of proxy responses. The response rate was not high, however, because of the refusal of next-of-kin to answer questions about deceased relatives and lack of attempt to locate next-of-kin to answer questions about some subjects who had died or moved away from Hiroshima or Nagasaki. The dependence on proxy respondents raises questions about the validity of the exposure data for some measures, particularly in childhood, and about

detailed information such as the number of cigarettes smoked per day, duration of smoking habit, and years since cessation of smoking. Information on childhood exposure was obtained for only two-thirds of the subjects. The omission of data on subjects where the next-of-kin had refused response or the subject had moved may be a source of bias. The diagnosis of lung cancer was not pathologically confirmed in over 40% of the cases. Even if the data were complete and accurate on all subjects, however, it is not clear that the subjects are representative of the target population. They had been exposed to ionizing radiation to varying degrees, whatever implication that may have; they are among the survivors, which may suggest selective characteristics; and their age distribution is high, ranging from about 35 to 90 years of age with an average of 70 or more years.

Only ever-marrieds are included in the ETS subjects, which is helpful in the analysis. There is some ambiguity in the statistical analyses, however, in reference to Tables 2 through 6 (the main results). The tables contain odds ratios that are reported to be the result of logistic regression with matching. The details regarding matching in the analysis are not given, but it is reported that analysis of the crude data and matched logistic regression give similar values. Regarding the analyses for trend, the outcome seems to be sensitive to the measure of exposure used. The odds ratio are strictly increasing for stratification by number of cigarettes smoked per day, but a different pattern emerges when ETS exposure is measured by the number of years the husband smoked cigarettes.

In general, the conclusions are presented more strongly than the data warrant. The assertions are somewhat tenuous that risks tend to increase with amount smoked by the husband, are highest among those who worked outside the home and whose husbands are heavy smokers, and decrease with cessation of smoking. Conversely, whereas little association between ETS exposure in childhood and lung cancer is reported, relevant information was available for only two-thirds of the subjects, and its accuracy is questionable because most of that information was provided by proxies. Overall, the observed data suggest that ETS exposure may be related to risk of lung cancer, but there is some potential for misclassification and other sources of bias. Thus, this study provides some useful information on lung cancer risk in passive smokers, but its interpretation needs to be more conservative, taking into account the atypical characteristics of the subjects and other concerns described above.

A.3. BROW

A.3.1. Author's Abstract

"The relation between various risk factors and adenocarcinoma of the lung was evaluated in a case-control study. Subjects were selected from the Colorado Central Cancer Registry from 1979-82 in the Denver metropolitan area. A total of 102 (50 males and 52 females) adenocarcinoma case interviews and 131 (65 males and 66 females) control interviews were completed. The control group consisted of persons with cancers of the colon and bone marrow. The risk estimates associated with cigarette smoking were significantly elevated among males (odds ratio [OR] = 4.49) and females (OR = 3.95) and were found to increase significantly ($p < 0.01$) with increasing levels of cigarette smoking for both males and females. For adenocarcinoma in females, the age- and smoking-adjusted odds ratios at different levels of passive smoke exposure followed an increasing overall trend ($p = 0.05$). After additional adjustment for potential confounders, prior cigarette use remained the most significant predictor of risk of adenocarcinoma among males and females. Analysis restricted to nonsmoking females revealed a risk of adenocarcinoma of 1.68 (95% confidence interval [C.I.] = 0.39-2.97) for passive smoke exposure of four or more hours per day. Neither sex showed significantly elevated risk for occupational exposures, although males bordered on significance (OR = 2.23, 95% C.I. = 0.97-5.12). The results suggest the need to develop cell type-specific etiologic hypotheses."

A.3.2. Study Description

This study was conducted in Denver, Colorado, to evaluate the role of smoking, passive smoking, occupation, community air pollution, and socioeconomic status in the etiology of adenocarcinoma of the lung. Because subjects include active smokers, the data on ETS subjects are part of a larger data set.

Cases and controls were drawn from the Colorado Central Cancer Registry. All subjects were diagnosed with lung adenocarcinoma between 1979 and 1982. Cases are white female Denver residents of at least 6 months' duration. Controls are of similar description to the cases, except that they were diagnosed with colon cancer or bone marrow cancer. Controls were matched on a group basis to produce the same age and gender composition. It is not clear if incident cases were used and whether control sampling was cumulative or density.

The subjects are not matched on smoking status, so the data on ETS subjects alone are unmatched for all variables considered in the larger study. Face-to-face interviews were conducted, blindly, on a total of 149 cases and 169 controls, after attrition in selection and follow-up of 47 cases and 38 controls. The subject was interviewed in 31% of the cases and 61% of the

controls; the remaining interviews were conducted with a friend or relative. The mean age of the female cases (controls) was 64.9 (68.2) years; no further details are provided. Clinical verification of lung cancer diagnosis was conducted microscopically.

"Exposed" to ETS is used in two ways, depending on context: (1) the husband smoked (presumably "ever-smoked" is intended, rather than "currently smokes," but that is not explicit); (2) the subject was in the presence of tobacco smoke, from any source, 4 or more hours per day on average. Although there are two operational definitions of exposure, neither includes duration of ETS exposure. Questions were apparently asked regarding exposure in both childhood and adulthood, the latter including sources in the home and in the workplace. No indication was found that the data collected from subjects was checked for internal consistency or against other sources. No mention was found regarding the number of unmarried women in the study or what assumptions may have been made regarding their exposure to ETS when spousal smoking is the source considered (the first of the definitions given above).

The ETS subjects consist of 4 out of 19 (exposed/total) female cases and 7 out of 47 controls, when ETS exposure means the spouse smoked (Definition 1). For exposure from all sources (Definition 2), the corresponding numbers for cases and controls are 4 out of 19 and 6 out of 47, respectively. The crude odds ratio is 1.52 (95% C.I. = 0.39-5.96) for Definition 1 of ETS exposure and 1.82 (95% C.I. = 0.45-7.36) for Definition 2 (data communicated from first author, Brownson). A test for trend using hours per day as the exposure measure is conducted on the whole data set for females *including smokers* (33 of 52 cases are smokers and 19 of 66 controls are smokers; the two exposure categories, 4 to 7 and 8 or more hours per day of exposure to passive smoke, contain a total of only 4 cases and 6 controls who are nonsmokers, but 19 cases and 7 controls who are smokers). The method of Miettenen is applied with stratification on age and smoker status ($p = 0.05$ for trend). The data for never-smokers alone were used in a multiple logistic regression to compare subjects exposed 0 to 3 hours per day with those exposed from all sources 4 or more hours per day (Definition 2 of ETS exposure). Adjustments were made for age, income, and occupation. The reported odds ratio is 1.68 (95% C.I. = 0.39-2.97). (*Note:* It appears that the upper confidence value may be in error. In view of the outcome for the crude odds ratio, a value about twice what is shown might be anticipated.)

To summarize the statistical tests and authors' conclusions, no significant risk estimates were shown when smoking by the spouse was considered as a dichotomous variable. When the data for both active smokers and passive smokers were stratified according to level of passive smoke exposure, a statistically significant trend in the risk estimates was shown for females ($p = 0.05$) after adjustment for age and cigarette smoking. However, after adjustment by logistic

regression for age, income, occupation, and cigarette smoking, with the two exposure categories for ETS combined (> 3 and 4+ hours per day), no significant risk was detected.

A.3.3. Comments

The study is very small when reduced to the never-smokers alone. The measure of ETS exposure used (hours/day from all sources) is not very specific to differentiate exposed from unexposed persons, particularly exposure 20 to 30 years ago, which may be more relevant than current exposure. Only 15% of the controls have a husband who smoked; only 13% of ETS subjects are exposed from any source 4 or more hours per day. Thus, the cut-point selected by the researchers for general ETS exposure (4+ hours/day) may be too high, resulting in a substantial amount of exposure in the "unexposed" group. For either definition of ETS exposure, however, the percentage exposed is extremely low. Details are lacking also in other areas that may have a bearing (e.g., the treatment of unmarried subjects—whether they were present and, if so, the assumption made regarding ETS exposure).

We experienced some difficulty with the statistical analyses. One of the adjusted procedures is the trend test. Perhaps because the number of ETS subjects is so small, smokers were included in the analysis and then a method was used to attempt to adjust the effects of their presence on the outcome. The only value that leaving the smokers in the analysis would serve, that we can see, would be if one believes that they contribute to the evidence on lung cancer and passive smoking. That seems doubtful. There are so few ETS subjects in the exposure categories (see above) that it seems highly unlikely that a test for trend would be significant if based on the ETS subjects alone (we did not have the number of ETS subjects by exposure group, however, so we were unable to conduct the trend test to check the outcome).

When the two exposure categories were combined and only the ETS subjects used, the results were not close to statistically significant (OR is 1.68; 95% C.I. = 0.39-2.97). We also had a problem with that result. When a statistical procedure is used to determine which variables to adjust for in using another procedure with the same data, it may distort the statistical interpretation. There also may be a typographical error in the upper confidence limit because the value shown is only about half the corresponding value for the crude odds ratio.

The remaining analyses are from the crude odds ratio, 1.52 (95% C.I. = 0.39-5.99) and 1.82 (95% C.I. = 0.45-7.36), which suggests a possible association between ETS exposure and lung cancer, although it could easily be ascribed to chance in view of the wide confidence intervals. The study has a very strict requirement for classification as exposed to ETS (4+ hours per day), which is reflected in only 15% of the controls being designated as exposed (40-60% is more

typical). The 12% figure based on simply being married to a smoker, however, is no better. The control subjects are unlikely to be a representative sample of the target population, or else the classification of subjects exposed is too rigid. The crude odds ratio may be the preferred statistical measure to represent the outcome of the data, but care should be exercised in using the results from this study in conjunction with those of other studies.

A.4. BUFF

A.4.1. Author's Abstract

"A population-based case-comparison interview study of lung cancer was conducted from 1979 to 1982 in six Texas coastal counties—Orange, Jefferson, Chambers, Harris, Galveston, and Brazoria—to evaluate the association of lung cancer with occupational and other environmental exposures. Lung cancer mortality rates in these counties consistently have exceeded lung cancer mortality rates observed for Texas and the United States from 1950-69 to 1970-75 for both sexes and races (white and nonwhites).

Histologically and cytologically confirmed incident cases diagnosed during the interval July 1976 to June 1980 among white male and female residents ages 30 to 79 years were ascertained from participating hospitals in the six-county area. Both population-based and decedent comparisons were selected and matched on age, race, sex, region of residence, and vital status at time of ascertainment. The exposures of primary interest in the study of lung cancer are those associated with occupation (employment in specific industries and occupations) in conjunction with tobacco, alcohol, diet, and residential exposures."

A.4.2. Study Description

This population-based case-control study was conducted in six coastal counties of eastern Texas to evaluate the association of lung cancer with occupational and other environmental exposures. Those of primary interest are associated with occupation in conjunction with tobacco, alcohol, diet, and residential exposures. The ETS subjects are part of this larger study that includes active smokers.

Cases include males and females ascertained from hospital and state records during 1976-80, except for Harris County, which includes only females from 1977-80. All subjects are white (including Hispanic) county residents of at least 6 months. Cases are incident, without restriction to cell type, and histologically diagnosed to eliminate secondary lung cancers (there is some inconsistency in the article on whether all diagnoses were by histology or whether some were by cytology). Controls were selected from State and Federal records, group matched on age, sex,

race or ethnicity, county of residence, and vital status. The candidate sample size is estimated in the report at approximately 1,650, including both sexes, of which just over 700 were lost to attrition in selection or follow-up for various reasons. Face-to-face interviews were conducted, a large number of which were with next-of-kin as necessitated by inclusion of decedent cases and controls. For example, for females, the number of subject interviews is only 18% for cases (81/460) and 24% (116/366) for controls. The distribution of ages is similar for cases and controls, based on groupings of 10-year intervals.

"ETS exposed" means having ever lived with a household member who smoked regularly. Exposure sources include the home environment during childhood and adulthood but excludes the workplace. There is no mention of whether data on ETS exposure were cross-checked with other interview questions or other sources. No indication was found regarding unmarried females in the sample and how marital status may affect level of exposure to ETS. Some summary information is provided on the distribution of tumors by cell type, but totals include smokers, so they are not reproduced here. The ETS data for females consists of 33 out of 41 (exposed/total) cases and 164 out of 196 controls; for males, the respective figures are 5 out of 11 and 56 out of 90. For the exposure definition given above, the crude odds ratio reported is 0.78 (95% C.I. = 0.34-1.81) for females (direct calculation from the data yields a value of 0.81; Buffler apparently added 0.5 to all cells to compensate for inclusion of no subjects in some cells). Little difference was found when female smokers were categorized by number of years lived with a household member who smoked. No adjusted statistical analysis is provided to account for variables used in matching for the study as a whole, nor is there a test for trend. The authors conclude that no effect of passive smoking is indicated for lung cancer. No attempt is made to evaluate whether exposure to ETS in childhood or adulthood is a factor.

A.4.3. Comments

The potential relationship between ETS exposure and lung cancer risk was not a principal issue in the design of this study. As described in the abstract, and more fully in the study description above, other potential etiologic factors were of more central concern. There are several limitations regarding the study's contribution to the epidemiologic evidence on ETS exposure and lung cancer risk. For example, the interview question on exposure to ETS is not very specific. "Having lived with a household member who smoked regularly" does not distinguish between exposure in childhood and in adulthood, between substantial and only light exposure, or between short-term and long-term exposure. One might expect a high percentage of persons to qualify as "exposed" under such a broad definition, and that is what the study demonstrates: 84%

of the controls are classified as exposed. With such a high percentage, both cases and controls may include a number of subjects who have experienced very light exposure to ETS. Another concern in this study is the use of decedent subjects. The majority of both male (86%) and female (82%) cases in the study (including smokers) were deceased. Consequently, a very high percentage of interviews was by proxy (82% of cases and 76% of controls).

This study was conducted in a region with a significantly higher age-adjusted mortality rate for lung cancer than for the United States in general. For all ages combined, the overall excess lung cancer mortality in the Texas study area is approximately 30% to 40% and is considerably higher for some age groups, according to the article. This was the apparent motivation for the study, with emphasis on important occupational and industrial exposures for residents of the Texas coastal area, including those associated with shipbuilding and repair, chemical and petrochemical manufacturing, petroleum refining, construction, and metal industries. If these nonsmoking factors affect the incidence of lung cancer, then they may be confounding the attempt to detect an effect from passive smoking. Appropriate statistical methods need to be applied to adjust the effect of each risk factor for the others.

Other factors may affect the ETS analysis also. Harris County, which is frequently addressed in the article in distinction to the other five counties, was apparently added to the study later (case ascertainment began 1 year later there and included only females; 10 of the 11 hospitals that did not participate are in Harris County). Consequently, there are some regional differences in the study as well as ethnic and racial differences (white and Hispanic). Although the authors took care to match controls on these and other factors, the matching only applies to the whole study (91% and 97% of male and female cases, respectively, are classified as having smoked regularly), not to the ETS subject group specifically, and there is no adjustment for these factors in the analysis. This potential confounding, the insensitive indicator of ETS exposure, and the large use of decedent cases and proxy responses limit the value of this study toward detecting any health effects associated with passive smoking.

A.5. BUTL(Coh)

This study was undertaken to explore the role of active and passive smoking in Seventh-Day Adventists in California. Subjects were participants in a larger prospective cohort study of factors affecting health in Adventists.

In 1974 the Adventist Health Study was initiated with the purpose of investigating the associations of a number of lifestyle and nutritional factors with morbidity and mortality in California Seventh-Day Adventists. Registered Adventist households were identified by

contacting the clerks of all 437 California Adventist churches. A basic demographic questionnaire sent to all households received a response rate of 58%. In 1976, all subjects aged 25 or older in 1974 were asked to complete a lifestyle questionnaire that included many demographic, medical, psychological, and dietary variables. Over two-thirds of the targeted subjects responded. From the non-Hispanic whites among these respondents, Butler and his colleagues drew two cohorts. One consisted of 22,120 spouses married and living together at the time of completion of the lifestyle questionnaire in 1976 ("spouse pairs") and the other of 6,467 individuals participating in an Adventist Health Smog Study of air pollution and pulmonary disease (the "ASHMOG" cohort); about two-thirds of the ASHMOG cohort was also included in the spouse-pairs cohort.

Subjects received annual forms for self-reporting of hospitalizations in the past year. Medical records relating to reported hospitalizations were then reviewed. Mortality was traced in four ways: linkage with California Death Certificate and National Death Index Systems, church clerk notification of deaths entered in church records, and follow-up of hospitalization history form responses (or nonresponses). Underlying and contributing causes of death were obtained from death certificates. Death certificates were obtained for all reported fatalities.

For the spouse-pairs cohort, subjects were considered unexposed to ETS if their spouses were either never-smokers *or* ex-smokers baptized into the Adventist church—which proscribes tobacco usage—before marriage. Those whose spouses were ex-smokers with less than 5 years of total smoking were also considered unexposed. All other subjects with ex- and current smoker spouses were classified as exposed.

Incidence rates were calculated using person-years. In the spouse-pairs cohort, age-adjusted lung cancer mortality rates for females married to past or current smokers were higher than those for female spouses of never-smokers, yielding relative risks of 1.94 and 2.47 for past and current smokers, respectively. Comparison of wives with ever- versus never-smoking husbands yielded a relative risk of 2.0. The same age-adjusted relative risk resulted when analyses were restricted to the 9,207 never-smoking females included in the spouse pairs. Virtually identical risk estimates resulted from both Mantel-Haenszel and Maximum Likelihood analyses. None of the relative risks was statistically significant at the 5% level.

In the ASHMOG cohort, the relative risk of lung cancer adjusted for age and past smoking status among females was 1.16 for women who had lived with a smoker for at least 11 years compared with women who had not lived with a smoker; no difference was observed for women who had lived for less than 11 years with a smoker, although this group was only one-tenth as large as the others. A similar pattern was seen among males who had lived for at least 11 years with a smoker, with an adjusted relative risk of 1.17.

In the spouse-pairs cohort, age-adjusted rates of smoking-related cancers (excluding lung cancer) were only slightly higher among nonsmoking females married to smokers than among nonsmokers (RR = 1.06); the relative risk rose to 1.22 when lung cancers were included.

In the ASHMOG cohort, age-adjusted rates using conditional maximum likelihood analysis for all smoking-related cancers were higher among males who lived with a smoker (RR = 1.45 for 1-10 years; 1.74 for 11+ years) or worked with a smoker (RR = 2.62 for 1-10 years; 1.47 for 11+ years). Among females, in contrast, only one (at RR = 1.03) of the four exposed categories had a higher rate than the nonexposed groups.

All lifestyle questionnaires were administered anonymously, thus reducing the potential for inaccurate responses caused by fear of discovery; respondents to the special supplemental ASHMOG questionnaire were assured of confidentiality but not anonymity.

Although causes of death were obtained from death certificates, review of medical records revealed histological confirmation in 99% of the primary malignancies reported among the spouse-pairs cohort. Thus, substantial misclassification of lung cancer deaths is unlikely. Subsequent study of patients discharged from 1 of the 11 participating Adventist medical centers over a 6-month period indicated that under 2% of study participants failed to report their hospitalizations; serious underascertainment of cases thus also seems unlikely. Losses to follow-up by study's end totaled only 1.2% of the original study cohort—a very low rate.

Comparing the results of the 1976 questionnaire with those of a supplemental questionnaire given to ASHMOG subjects in 1987, 4.7% of male smokers now reported themselves as "never-smokers" and 1.4% of never-smokers now reported themselves as nonsmokers. Concordance of female responses was even higher. This concordance of responses does not necessarily imply the degree of *accuracy* of responses, only their reliability.

Comparison of responses to the 1987 questionnaire by females revealed that about 6% of those previously classified as not having a smoking spouse now reported having had one; the converse was also true for 6% of the women. These data indicate a mild nondifferential misclassification of exposure, which would push results toward the null.

Information is available on a large number of variables of possible interest as potential confounders or risk mediators. Unfortunately, the modest number of total lung cancer deaths among females in the spouse-pairs cohort (8) or among both sexes in the ASHMOG cohort (13) discourages attempts to control for other potential confounders in addition to age in the analyses. Separate consideration of the association between variables other than passive smoking and age-adjusted lung cancer mortality among women indicated a high relative risk (RR > 4) for spousal blue collar occupation. No other variables produced nearly as strong or consistent an association;

in fact, the only other consistent association was a relative risk of 1.3 to 1.6 for nonrural status. Unfortunately, no breakdown of blue collar spousal status by exposure groups was presented.

By virtue of its basic design, the inherent minimization of sources of confounding provided by its study population and the level of information available regarding potential confounders, and other sources of bias, the Butler study has many of the key ingredients to produce convincing results. Unfortunately, this potential goes largely unrealized because of the low number of outcome events occurring during the follow-up period, which for the most part renders stratification or control for multiple factors simultaneously impractical; even stratification by several age or exposure levels produces unstable results.

Nevertheless, the findings of this study are quite consistent with the hypothesis that ETS exposure of nonsmokers is associated with mildly elevated lung cancer, (active) smoking-related cancer, and ischemic heart disease mortality. Insofar as the study data allow for consideration of potential misclassification and confounding effects, neither misclassification nor confounding can account for the observed association. Because of the limited number of outcome events, several possible confounding factors could not be definitively or adequately addressed in the analyses and the observed associations were not statistically significant, the study's findings must be viewed as suggestive but not of themselves convincing.

A.6. CHAN

A.6.1. Author's Abstract

(*Note:* This study is described in two sources, both of which were used for the description below. Chan et al. [1979] is the more complete description, but it contains considerable attention to active smoking as a cause of lung cancer. Chan and Fung [1982] is a condensed version that specifically addresses nonsmokers. The abstract given here is for the 1979 article. No abstract is provided in the 1982 source.)

"Bronchial cancer is a disease of high and increasing annual incidence in Hong Kong, especially in women, whose age-specific death rates from this cause are amongst the highest in the world. A case-control study of the relationship of bronchial cancer with smoking was carried out during 1976-77, taking particular note of the histological type of the tumour. Two hundred and eight male and 189 female patients were interviewed, covering about half the total number of cases of bronchial cancer registered as dead from the disease in Hong Kong during the period of survey. The association with smoking was more evident in males than in females, and in squamous and small-cell types, as a group, than in adenocarcinoma. Forty-four per cent of the women with bronchial cancer were non-smokers, their predominant tumour being

adenocarcinoma, and in them no association could be detected with place of residence or occupation. There was no strong evidence of an association with the use of kerosene or gas for cooking; 23 did not use kerosene. The cause of the cancer in these nonsmoking women remains unknown."

A.6.2. Study Description

(*Note:* This description is primarily based on Chan et al. [1979]. Chan and Fung [1982] are cited when used as a reference.)

This study is the earliest of four from Hong Kong that consider ETS exposure as a potential etiologic factor for lung cancer incidence in nonsmoking women. Here, however, that objective is secondary to evaluation of the relationship of bronchial cancer with active smoking.

In the whole study, target cases are the lung cancer patients, male and female, in five hospitals in Hong Kong during 1976-77 that were willing and able to be interviewed. Controls are patients of the same general age groups from the orthopedic wards of the same hospitals as the cases. No specific diseases are excluded. Cases are incident and control sampling is density. The candidate sample size is 208 (189) male (female) cases and 204 (189) male (female) controls. Attrition from selection or follow-up is not reported but appears high. Subjects were personally interviewed, as possible. About half of the estimated number of lung cancer cases diagnosed in Hong Kong during the study period were actually interviewed. Some patients were too ill to answer questions, and more than expected were treated elsewhere than in the hospitals covered. No interviews with next-of-kin were obtained for the cases interviewed.

The ETS subjects (never-smokers) alone include 84 (2) female (male) cases and 139 (30) female (male) controls. The age distribution of the female cases (controls) is, by percentage, as follows: age less than 40, 7 (5%); ages 40 to 49, 15 (15%); ages 50 to 59, 23 (30%); ages 60 to 69, 23 (22%); and age 70 or more, 32 (28%). Cases with a histological diagnosis were reviewed and verified by reexamination of the pathological specimens. In the absence of a histological specimen, cytological diagnosis was accepted. In some cases, on histological grounds, secondary adenocarcinoma was suspected, and a few cases were rejected after detailed examination of the clinical records. Of the cases, 46 (55%) were diagnosed by histology, 23 (27%) by cytology, and 15 (18%) by radiology and clinical means. Diagnoses by cell type were as follows: squamous or small cell, 19 (22%); adenocarcinoma or large cell, 40 (48%); others and unspecified, 25 (30%). Of the unspecified, 15 had no histological or cytological verification.

ETS subjects are never-smokers. Classification of a subject as exposed or unexposed to ETS is based on the response to these questions: (1) If you do not smoke, have you been exposed

to cigarette smoke from other people at home or at work? (2) Does your husband/wife smoke? (If "yes," how many cigarettes per day?) (The first question is included in Chan et al., 1979. The second one is from a communication of Linda C. Koo.) No information is reported on the distribution of tumors by central and peripheral location.

The ETS data on females based on question 1, above, consists of 50 out of 84 (unexposed/total) cases and 73 out of 139 controls. The authors state that "this is a rather subjective approach to the problem." No statistical estimates are provided; our calculation of the crude odds ratio is 0.75 (95% C.I. = 0.43-1.30). No clear conclusion is drawn regarding the potential relationship between ETS exposure and lung cancer occurrence, but the authors imply that no connection was found (which the odds ratio and confidence interval amply support). The authors found no particular occupation as being dangerous. Their findings also do not support air pollution as a factor, and they provide no strong evidence that cooking with various types of fuel is relevant.

A.6.3. Comments

Although data on spousal smoking were collected along with an indication of the number of cigarettes smoked per day, they are referred to only in the 1982 article, where the authors note without further elaboration that more nonsmoking cases have nonsmoking spouses. It is reported that answers to the question, "Are you exposed to the tobacco smoke of others at home or at work?" gave no indication that other people's smoking was a risk factor for lung cancer in nonsmokers, with 40.5% of cases and 47.5% of controls answering yes to this question. Why the data for spousal smoking are not given and analyzed is unknown. The question about general ETS exposure combines sources in the household and workplace and refers only to current exposure without a measure of duration, which would likely affect any risk associated with passive smoking.

Although it is reported that cases and controls are similar in age, occupation, and other characteristics, comparability is questionable. The article cites a criticism of the whole study (including smokers) for use of orthopedic patients as controls, on the basis that some patients may be hospitalized with smoking-related diseases (e.g., osteoporosis). It was found that the controls smoke more than a group representative of the population of Hong Kong. This would create a bias toward negative association. Although these comments refer to smoking habits, they suggest the potential for selection bias of controls that may extend to nonsmoking controls as well.

It is noted, also, that there are more cases from Hong Kong Island than would be expected from the population distribution of Hong Kong as a whole, possibly due to more success

contacting cases in Hong Kong Island than in Kowloon. The authors caution about reaching any conclusion about the distribution of cases within Hong Kong as a whole. The failure to follow up on patients who were eventually treated at other hospitals or were too ill to be interviewed is, of course, a potential source of bias itself.

Other differences are apparent between cases and controls. Among nonsmokers, a higher percentage of cases than controls (1) are Cantonese (81 vs. 70) or (2) have ever cooked with kerosene (73 vs. 60). It is speculatedthat the Cantonese diet, high in nitrite or nitrate content, may be a factor in lung cancer incidence (Chan and Fung, 1982). More broadly, these comparisons between cases and controls indicate differences in ethnic composition, lifestyle, and socioeconomic status that are difficult to assess.

In summary, ETS subjects are not matched in the design, and an adjusted statistical analysis is not conducted. Consequently, potential sources of bias and confounding are not controlled. There is substantial basis to question the comparability of cases and controls, as described above. Data quality is suspect because confirmation of primary lung cancer was limited and cases were missed because patients were too ill to be interviewed personally or were eventually treated at another hospital. Also, the question posed to subjects for classification as exposed or unexposed to ETS is sufficiently general to invite subjective response. Overall, methodological shortcomings hamper interpretation of this study's findings, rendering its conclusions questionable.

The finding that spousal smoking appears to be more frequent in controls, mentioned in the 1982 report, is noted to be at variance with the Hirayama study, which may have motivated the authors to conduct this secondary analysis of ETS exposure using their previously collected data. Whatever the motivation, the original study is rather limited as a source to evaluate passive smoking. Overall, this study does not reflect as much care and attention to detail as would be useful, limiting its value for assessing ETS exposure and lung cancer.

A.7. CORR

A.7.1. Author's Abstract

"Questions about the smoking habits of parents and spouses were asked in a case-control study involving 1,338 lung cancer patients and 1,393 comparison subjects in Louisiana, USA. Nonsmokers married to heavy smokers had an increased risk of lung cancer, and so did subjects whose mothers smoked. There was no association between lung cancer risk and paternal smoking. The association with maternal smoking was found only in smokers and persisted after controlling for variables indicative of active smoking. It is not clear whether the results reflect a biological

effect associated with maternal smoking or the inability to control adequately for confounding factors related to active smoking. This preliminary finding deserves further investigation."

A.7.2. Study Description

This study was conducted in Louisiana to investigate the relationship of smoking habits of parents and spouses to lung cancer occurrence. Results of the study were published in 1983; some clarifying details regarding study methodology were supplied in a 1984 paper addressing only the effects of active smoking. The accrual period is not stated; cases are probably a mixture of prevalence and incidence, and controls are cumulatively sampled. ETS subjects constitute a small portion of the whole study, which includes active smokers.

Cases consist of patients diagnosed with primary lung cancer, exclusive of bronchioalveolar carcinoma, from participating hospitals in several Louisiana parishes (counties), predominantly in the southern part of the state. A total of 302 female and 1,036 male cases and an equal number of controls are included in the whole study. Controls were selected from other patients, excluding those diagnosed with emphysema, chronic bronchitis or obstructive pulmonary diseases, or certain cancers (laryngeal, esophageal, oral cavity, and bladder). They were matched to cases on hospital, age ($\pm$ 5 years), sex, and race. Information about active and passive smoking was obtained by interview (presumably face to face and unblinded), with responses obtained from next-of-kin in 24% of cases and 11% of controls; no information on refusals is provided. ETS subjects were identified by exclusion of individuals who had ever smoked or had never been married, which eliminated 279 female and 1,026 male cases. Removal of subjects with no spousal smoking data eliminated one additional female and two male cases, leaving 22 female and 8 male cases. Similarly, a total of 1,080 men and women were excluded from controls. No demographic comparisons are given, either for the whole study or for the ETS subjects alone, nor is the number of proxy responses provided for the ETS subjects. Histological confirmation was obtained for 97% of cases in the whole study, including ever-smokers.

"ETS exposed" is used in two ways, depending on the analysis given: (1) the spouse has smoked at least 1 pack-year of cigarettes or (2) the spouse currently smokes. Units of exposure are pack-years and current consumption is in cigarettes per day for (1) and (2), respectively. ETS exposure in childhood means that at least one parent smoked during most of the subject's childhood. Types of tobacco smoking other than cigarettes (e.g., cigars and pipes) are referenced indirectly in regard to interview questions but are not included in the data analysis. Other sources of exposure, either at home or in the workplace, are not considered. Never-married women are excluded from ETS analysis, but no information is given on the number of nonsmoking widows

and divorcees and how they were handled with regard to ETS exposure. Adenocarcinoma accounts for 54% of lung cancers in nonsmoking women, compared to 22% in women who actively smoke. No further histological breakdowns are provided.

For the main analysis of spousal smoking, exposure constitutes one or more pack-years of spousal cigarette consumption. ETS-exposed subjects include 14 (61) of 22 (133) female cases (controls) and 2 (26) of 8 (180) male cases (controls). These data yield a crude odds ratio of 2.07 (95% C.I. = 0.81-5.25) for females (confidence interval was calculated by reviewers). Among females, stratification by 0, 1 to 40, and 41 or more pack-years of exposure yields odds ratios of 1.0, 1.18, and 3.52, respectively, with the highest exposure category being statistically significant at $p < 0.05$. No adjusted results are presented. It is, however, reported that analyses based on current daily spousal cigarette consumption produced very similar results to the pack-year analyses. In addition, it is reported that neither exclusion of proxy interview data nor restriction to same-race subjects significantly alters the results. Analysis of parental smoking during childhood embraces the combined population of smokers and nonsmokers, adjusting for smoking status by logistic regression. Maternal smoking is associated with significantly increased estimated risk of lung cancer (OR = 1.38, $p < 0.05$) but paternal smoking is not (OR = 0.83). No association was noted among nonsmokers alone, but the authors note that small numbers preclude adequate analysis of this group.

A.7.3. Comments

The study entails a major multicentric effort to assemble hospital-, age-, race-, and sex-matched lung cancer cases and controls from Louisiana hospitals. Its use of trained local interviewers familiar with the region's culture increases the probability of obtaining accurate interview data for the nearly 3,000 subjects involved. Exclusion of active smokers to assess ETS exposure, however, exacts a toll on the study's power and validity. Because the initial matching of cases and controls did not include smoking status, the ETS subjects are unmatched in the analyses of spousal and parental smoking. This potential problem is not addressed by the authors. The lack of any demographic information on cases and controls leaves the comparability of these groups uncertain.

The potential problem of misdiagnosis of primary lung cancer is minimized by the high rate (97%) of histological case confirmations. Eligibility criteria for controls were intended to exclude smoking-related diseases. Some 15% of the controls had cardiovascular disease, however, which has been associated with both active and passive smoking. The authors also speculate that the inclusion of adenocarcinoma, reportedly less smoking-associated than other lung cancers, may

have diluted the significance of their results, but they do not present analyses using their extensive histological data to assess this question.

Restriction of the spousal smoking analysis to ever-married individuals eliminates potential confounding by differences between lifelong single and married individuals. Stratification by gender controls for any sex-related differences. Both race and proxy interview were reported to have no effect on the spousal smoking results, and the spousal smoking association was still observed after division of women into over and under 60 years of age. A small number of nonsmoking ever-married cases (8 males and 22 females for this study) hampers efforts to control statistically for confounders; nonetheless, direct adjustment for age and race is needed. There are other potential confounders not controlled for, such as socioeconomic status, diet, and other sources of smoke exposure.

It is concluded that females married to heavy smokers have an increased risk of lung cancer. A significant increase in risk for nonsmokers was found from maternal but not from paternal smoking in childhood. The results for childhood exposure, however, use statistical methods to adjust for the presence of active smokers instead of removing the data for them prior to analysis. This gives the *appearance* of increasing an otherwise small sample size (the ETS subjects alone) to attain significance, at the risk of biased results. The potential for bias in all of the analyses, which could be in either direction and may or may not be of consequence, needs to be kept in mind when using this study's results.

A.8. FONT

A.8.1. Author's Abstract

"The association between exposure to environmental tobacco smoke (ETS) and lung cancer in female lifetime never-smokers was evaluated using data collected during the first three years of an on-going case-control study. This large, multi-center, population-based study was designed to minimize some of the methodological problems which have been of concern in previous studies of ETS and lung cancer. Both a cancer control group and a population control group were selected in order to evaluate recall bias. A uniform histopathologic review of diagnostic material was conducted for case confirmation and detailed classification. Biochemical determination of current exposure to tobacco and screening of multiple sources of information to determine lifetime nonuse were employed to minimize misclassification of smokers as nonsmokers.

A 30% increased risk of lung cancer was associated with exposure to ETS from spouse, and a 50% increase was observed for adenocarcinoma of the lung. A statistically significant positive trend in risk was observed as pack-years of exposure from spouse increased, reaching a relative

risk of 1.7 for pulmonary adenocarcinoma with exposures of 80 or more pack-years. The predominant cell type of the reviewed, eligible lung cancer cases was adenocarcinoma (78%). Results were very similar when cases were compared to each control group and when separate analyses were conducted for surrogate and personal respondents. Other adult-life exposures in household, occupational, and social settings were each associated with a 40% to 60% increased risk of adenocarcinoma of the lung. No association was found between risk of any type of lung cancer and childhood exposures from father, mother or other household members."

A.8.2. Study Description

This study was initiated in 1985 in five major U.S. metropolitan areas to investigate the association between exposure to ETS and lung cancer in female lifetime never-smokers. The study was designed specifically to address this issue and includes only never-smokers. The results reviewed are from an interim report, with the completed study expected to encompass an additional 2 years of case accrual.

Patients were English-, Spanish-, or Chinese-speaking female residents 20 to 79 years of age who have never used tobacco, have no prior history of malignancy, and have histopathologically confirmed primary lung cancer. The lung cancers were originally diagnosed at participating hospitals in Atlanta, Houston, Los Angeles, New Orleans, and the San Francisco Bay area, between December 1, 1985, and December 31, 1988. Two control groups were assembled, one from colon cancer patients and the other from the general population, with the same general eligibility requirements as cases. The population control group, consisting of women selected from the general population by random digit dialing and by sampling from Health Care Financing Administration files, were frequency matched on age (< 50, 50-59, 60-69, 70+), with two controls per case. The colon cancer controls were frequency matched to cases by 10-year age groups and by race. The lung cancer group consists of incident cases, but there is no indication whether density or cumulative sampling was employed for either control group. Exposure data were collected in face-to-face, apparently unblinded, interviews.

Extensive efforts were made to include only never-smokers. For cases and colon cancer controls, medical records were reviewed for tobacco use and physicians were contacted as necessary. Eligible cases not previously excluded and all population controls were contacted by telephone to screen for prior use of tobacco (no more than 100 cigarettes smoked or use of any tobacco in any form for more than 6 months). Urinary cotinine was bioassayed to eliminate any misreported current smokers.

A total of 514 eligible cases were identified, of which 83 were not interviewed for unspecified reasons and 2 had urinary cotinine levels consistent with active smoking. Independent histopathologic review by a pulmonary pathologist was performed for 84% (359/429) of the lung cancer cases, resulting in nine exclusions. Only the remaining 420 cases are included in the study. Colon cancers were not reviewed. Of 489 (1,105) eligible colon cancer (population) controls, 131 (311) were not interviewed and 7 (14) were excluded for high urinary cotinine. Proxies were interviewed for 143 (34%) of the lung cancer cases and 35 (10%) of the colon cancer controls, whereas no proxies were used for the population controls.

Cases and the two control groups all have similar age distributions, with the majority of subjects between 60 and 79 (73%, 74%, and 74% of the cases, colon, and population groups, respectively). The proportion of whites is similar across all groups (63-69%), but the control groups contain a somewhat higher proportion of blacks and lower proportion of other minorities, and a little higher percentage of high school graduates (76% and 79% vs. 68%). Cases and controls are comparable by metropolitan size of adulthood and childhood residences and also by annual income.

Four sources of adult ETS exposure are assessed: smoking by (1) spouse(s) and (2) other household members while living with the subject, and reported exposure to ETS in (3) occupational and (4) social settings. Three sources of possible exposure in childhood (up to 18 years of age) are considered: smoking by (1) father, (2) mother, or (3) other household member(s) while living in the subject's home for at least 6 months. Subjects are characterized as ever- versus never-exposed with a subanalysis by tobacco type (cigarette, pipe, or cigar). Years of exposure are also tabulated. In addition, cigarettes per day for spouse and for other household sources and pack-years for spouse(s) are calculated. No checks on exposure (aside from the cotinine screening) are reported.

Adenocarcinoma is the dominant type of lung cancer among study subjects, representing 76% (311/409) of all cases included in the study (with the exception of 11 cases with "review pending") and also 78% (281/359) of all independently confirmed primary bronchogenic carcinomas among those cases. Other cell types include 12% (48/409) large cell, 7% (27/409) squamous cell, 3% (14/409) small cell, and 2% (9/409) other cancers. No data on airway proximity are provided.

The final study population (for this interim report) consists of 420 lung cancer cases, 351 colon cancer controls, and 780 population controls. Exposure to spousal smoking from all types of tobacco is reported for 294 cases, 231 colon cancer controls, and 492 population controls, yielding similar odds ratios (adjusted for age, race, area, income, and education) of 1.28 (95% C.I. = 0.93-

1.75) and 1.29 (0.99-1.69) using the respective control groups. Elevated but statistically nonsignificant observed risks are also observed when cigarette, cigar, and pipe exposure are assessed separately, with either control group. Restriction of analyses to the 281 independently reviewed adenocarcinomas results in stronger associations, with adjusted odds ratios of 1.44 (95% C.I. = 1.01-2.05) and 1.47 (1.08-2.01) for all types of tobacco, and increased odds ratios for each type of tobacco as well.

Odds ratios were also calculated for ETS exposure from cigarette smoking alone, with the two control groups combined (the individual results using each control group are entirely consistent). For all lung cancer types combined, the adjusted odds ratios are 1.21 (0.96-1.54) for spousal smoking, 1.23 (0.97-1.56) for other household members, 1.34 (1.03-1.73) for occupational environments, and 1.58 (1.22-2.04) for social exposure, the last two of which are significant ($p <$ 0.05 and 0.01, respectively). The corresponding odds ratios for adenocarcinoma cases alone continue to be uniformly higher: 1.38 (95% C.I. = 1.04-1.82), 1.39 (1.05-1.82), 1.44 (1.06-1.97), and 1.60 (1.19-2.14). The odds ratio tends to increase over years of exposure for all carcinomas combined and for adenocarcinoma alone, although not monotonically (without downturns). The tests for upward trend are all significant or suggestive, with p-values ranging from < 0.001 to 0.07 (these p-values are half those reported, which apply to a trend in either direction). Finally, for spousal smoking measured in pack-years, the upward trend is significant for adenocarcinoma alone and for all lung cancers together ($p < 0.005$ and 0.04, respectively).

The authors interpret their findings as evidence of a causal relationship between ETS exposure in adulthood and lung cancer in never-smoking women. In contrast to adulthood, ETS exposure during childhood shows no association with lung cancer, for either all cell types combined or adenocarcinoma alone. Adjusted odds ratios tend to be slightly (but not significantly) below unity for all exposure sources.

A.8.3. Comments

This study is much larger than any other ETS case-control study. Over 400 never-smoking female lung cancer cases were enrolled in just over 3 years, in contrast to the 25 to 75 cases typical of most studies, and two control groups were formed, totaling over 1,200 subjects. Additionally, the cases and controls are drawn from five widely dispersed metropolitan centers in the United States, representing a population of approximately 18.5 million people, about 8% of the U.S. population. This characteristic increases the generalizability of the study and diminishes the potential for bias related to locale.

Extensive efforts were made to achieve precision and validity, in evidence throughout the study. Cases and controls are highly comparable. They are frequency matched on age and, for colon cancer controls, on race as well. The distributions of other demographic variables—annual income, childhood residence, and adult residence—are quite similar between cases and both control groups. The control groups contain a little higher (lower) proportion of blacks (Asians and Hispanics) and a higher percentage of high school graduates. These differences, however, should not have influenced the reported associations because all odds ratios are adjusted for race and education.

The use of incident cases reduces the potential for selection bias, and the implementation of two control groups allowed for assessment of potential bias from comparison with cancer patients or the general population alone. The similarity of results obtained from the two control groups suggests little bias from choice of controls.

The use of a multistep procedure to eliminate inclusion of former or current smokers reduces the potential for smoker misclassification as a source of upward bias. As a further safeguard, urinary cotinine was bioassayed for all consenting persons to exclude those likely to be current smokers. This is the only published study we are aware of to implement this precaution. Attention to histopathology is also very thorough. Inclusion of only histologically diagnosed primary carcinoma reduces the likelihood of diagnostic error, which is further reduced by the use of independent histopathologic review of most cases by a single pulmonary pathologist. The study's histopathologic findings bring out two interesting points. First, comparison of cell type diagnoses between hospital and independent reviewers revealed poor concordance for large (56%) and squamous (67%) cell carcinomas, indicating that cell-type-specific analyses for these cancers may be misleading, particularly if all diagnoses are not made by the same pathologist. The histopathologic review also resulted in a net increase of adenocarcinomas from 244 to 281, 78% of the total, a higher proportion than in most but not all other studies. The statistical results were stronger when limited to cases of adenocarcinoma alone.

Exposure information was obtained in the most reliable way, by face-to-face interviews with each interviewer trained and fluent in the subject's primary language. Information for a substantial proportion of lung cancer cases (34%) was obtained from proxy respondents, but fewer proxies were required for colon cancer controls (10%), and none were used for population controls. The use of proxy respondents raises the possibility of information bias, but their exclusion reportedly did not alter the study's findings. The apparent lack of blinding also raises the possibility of interviewer bias, but it is unlikely that such bias (or recall bias, for that matter)

would restrict its effect to adenocarcinoma. Also, the same relationships hold whether the colon cancer or population controls are used.

Particular attention is paid to all sources of ETS exposure, which is more informative than addressing only spousal smoking, with four sources in adulthood and three in childhood evaluated both individually and in combination. Additionally, subjects are counted as exposed to the ETS of a spouse or other household smoker only *while living with* the source, giving a more accurate account of exposure than simply determining whether a spouse or household member ever smoked. Consequently, the measures of ETS exposure are more specific by source, and probably more accurate, than in most studies. This reduces bias toward unity in the odds ratio arising from poor distinction between exposed and unexposed subjects. Still, further accuracy might have been achieved by stipulating that smoking must occur in the subject's household or presence, but this is a minor point.

Most of the standard potential confounders—age, race, geographic area, income, and education—are adjusted for in all analyses and thus can be ruled out as sources of the observed results. Although information on diet, occupational exposures, and "other exposures of interest" were collected, these factors are not addressed in this interim report. Thorough treatment of the issue of potential confounding by these factors will presumably be undertaken after subject accrual is finished and published in the completed study.

To summarize, this study was designed specifically and solely to address the topic of ETS as a potential lung cancer risk to nonsmoking women. Several issues were given special attention, such as the potential misclassification of smoking status, histopathologic specificity, recall bias, source of ETS exposure, and potential confounders and other risk factors. Histopathologic specificity has not been convincingly demonstrated in prior studies, and the meaning of "exposed to ETS" has differed widely between studies, even those addressing spousal smoking only. The remaining issues are largely related to controlling potential sources of bias and confounding to enhance validity. The qualitative rigor and completeness of detail in this study is impressive. In addition, it is quite large, which increases precision of estimates and power to detect an association, if it exists. Use of dietary, occupational, and other exposure data in the analyses, along with an additional 2 years of subject accrual, will make the completed study for which this constitutes an interim report even more valuable. As it stands, however, this study is already the largest and most useful case-control study available. Its high quality and the reasonable consistency of the evidence across sources of ETS exposure strongly support an increase in lung cancer incidence associated with passive smoking.

A.9. GAO

A.9.1. Author's Abstract

"A case-control study involving interviews with 672 female lung cancer patients and 735 population-based controls was conducted to investigate the high rates of lung cancer, notably adenocarcinoma, among women in Shanghai. Cigarette smoking was a strong risk factor, but accounted for only about one-fourth of all newly diagnosed cases of lung cancer. Most patients, particularly with adenocarcinoma, were life-long non-smokers. The risks of lung cancer were higher among women reporting tuberculosis and other pre-existing lung diseases. Hormonal factors were suggested by an increased risk associated with late menopause and by a gradient in the risk of adenocarcinoma with decreasing menstrual cycle length, with a 3-fold excess among women who had shorter cycles. Perhaps most intriguing were associations found between lung cancer and measures of exposure to cooking oil vapors. Risks increased with the number of meals cooked by either stir frying, deep frying or boiling; with the frequency of smokiness during cooking; and with the frequency of eye irritation during cooking. Use of rapeseed oil, whose volatiles following high-temperature cooking may be mutagenic, was also reported more often by the cancer patients. The findings thus confirm that factors other than smoking are responsible for the high risk of lung cancer among Chinese women and provide clues for further research, including the assessment of cooking practices."

A.9.2. Study Description

This study was undertaken in Shanghai, China, during 1984-86 to explore reasons for the high rates of lung cancer among women in Shanghai. Potential etiologic factors associated with the high occurrence of adenocarcinoma among females in a population where few women smoke cigarettes is of particular interest. Several potential risk factors, in addition to exposure to ETS, are investigated. These are included in the abstract above. Smokers are included in the study as well as nonsmokers.

A special reporting system for lung cancer linked with the area's medical facilities was set up for the study period, integrated with the Shanghai Cancer Registry. Incident cases of lung cancer occurring among 35- to 69-year-old female residents of urban Shanghai from February 1984 to February 1986 were interviewed by trained study personnel. Controls were women selected from residents of the urban Shanghai community by stratified random sampling designed to mimic the age distribution of Registry-reported lung cancer cases during 1980-81. It is not clear whether cumulative or density sampling was employed.

Face-to-face interviews were conducted with 672 cases and 735 controls. No cases refused to be interviewed, but 93 died before interview and were therefore excluded; it is not mentioned whether there were any refusals among potential controls. Nonsmokers composed 436 of the cases and 605 of the controls. In the total subject population, distribution of age, education, and marital status between cases and controls is described as similar, except for a larger proportion of controls (32% vs. 20%) in the oldest age group (65-69 years). The age distribution in the ETS population alone is not described.

ETS exposure is based on living with a smoker. For general exposure in childhood or adulthood, exposed subjects are those who ever lived with a smoker. For spousal smoking alone, however, women are ETS exposed only if they lived with a smoking husband for *at least* 20 years. General ETS exposure sources include all household members but not coworkers. Verification of exposure data was not mentioned. Based on the reported exposure criteria, widows and divorcees would have been included in the spousal smoking data set, whereas never-married women would have been excluded.

For ETS subjects, 246 (375) cases (controls) from the total of 672 (735) cases (controls) are included in Table II of the article that lists the number of cases and controls by number of years lived with a smoking husband. Presumably the 190 cases and 230 controls not included in the table are unmarried (or never-married) and do not include women married and living with a nonsmoker; no explanation is provided in the article.

Among nonsmoking women included in Table II, 189 out of 246 cases and 276 out of 375 controls had lived with a smoking husband for at least 20 years. These subjects were divided into exposure categories of 20 to 29, 30 to 39, and 40 or more years for comparison with the "unexposed" (< 20 years spousal smoking) subjects. The authors present no unadjusted analyses, but calculations from their raw data yield an overall odds ratio of 1.2 and stratum-specific odds ratios of 1.2, 1.3, and 1.1 for 20 to 29, 30 to 39, and 40 or more years of exposure, respectively. Age and education-adjusted odds ratios increase with the number of years exposed: 1.1 (95% C.I. = 0.7-1.8) for 20 to 29 years, 1.3 (0.8-2.1) for 30 to 39 years, and 1.7 (1.0-2.9) for 40 or more years. The authors report an odds ratio of 2.9 (1.0-8.9) for squamous and oat cell cancer for 40 years of exposure or less but present no other type-specific results.

Information on cell type is available for the 542 (81%) study cases diagnosed by histology or cytology; the rest of the cases were diagnosed by radiological or other means. Diagnostic evidence was reviewed by a team of pathologists and clinicians. For the lung cancer cases histologically typed, adenocarcinoma (61%) greatly predominates, followed by squamous (22%),

small cell (6%), and other (11%) types. No breakdowns of tumor type are provided for the ETS group.

The authors conclude that ETS may account for some, but probably few, of the cancers among nonsmokers, because there was little or no association with ever having lived with a smoker. Among nonsmoking women married to smokers, however, there was an upward trend in risk associated with increasing years of exposure. This latter finding is consistent with reports in other parts of the world. Little evidence was found to implicate the type of fuels used for cooking in lung cancer risk; occupational factors did not appear to be important, nor did familial tendency to lung cancer. Our data suggest, however, that prior lung diseases, hormonal factors, and cooking practices may be involved. Most provocative is the association with cooking oil volatiles, and further investigations are needed to evaluate their contribution to the high lung cancer rates among Chinese women in various parts of the world.

A.9.3. Comments

The number of ETS subjects for analysis is relatively large. Unfortunately, the study is unmatched, with no demographic breakdown of the cases and controls, either for the whole study or for the ETS subjects alone. Controls were selected to make their age distribution similar to that expected for cases in the whole study, but the similarity may not apply to ETS subjects alone. Consequently, there is little basis for evaluating the comparability of cases and controls. Age and education were adjusted for in the analyses, which has some compensatory value.

The use of direct interview with all subjects without reliance on proxies to gather exposure information should enhance the validity of the exposure comparisons. On the other hand, the possible use of unblinded interviewers could have biased results. In light of the lack of association noted for passive smoke exposure as a child or adult, however, it is unlikely that such a bias produced the observed association between spousal smoking and lung cancer. For evaluation of spousal smoking, the reference group can hardly be classified as "unexposed" to spousal smoking because it includes women who lived with a smoking husband for up to 20 years. The investigators probably selected the cutoff level of exposure for their spousal smoking reference group to balance the numbers in each exposure category, as a practical matter. The reference group contains an undisclosed number of women who may have been exposed to spousal smoking for many years, potentially creating a substantial bias toward the null hypothesis (no association between ETS exposure and lung cancer). Consequently, the odds ratios may be biased downwards. The relative comparison across years of spousal smoking, however, is not affected. An increasing trend in the odds ratio was observed, but no statistical test for trend is cited. In a similar vein, it

appears that active smokers *may* have been included in the data analysis of overall ETS exposure. That factor, in combination with the use of ever- versus never-exposed classifications without regard to degree or duration of ETS exposure in the analyses, may have reduced the likelihood of detecting any positive association that may exist.

The study appears to have focused on potential risk factors other than ETS. Unfortunately the effects of these other factors on the ETS results were not explored, even though many of these appeared to be stronger risk factors than passive smoking. Some potential confounding factors, such as age and education, *were* adjusted for in all analyses. Control for education should in turn produce a degree of adjustment for factors related to socioeconomic status (e.g., dwelling size and quality of diet).

Overall, the study presents evidence of a mild duration-dependent association between lung cancer and spousal smoking that skirts statistical significance. Several sources of misclassification bias are possible, but most would tend to bias the odds ratio downward. The study was not, however, specifically designed to evaluate the ETS-lung cancer hypothesis. Information was collected and analyzed on a number of other potential risk factors, but none of these besides age and education were considered as potential confounders. Coupled with other limitations, this omission reduces the weight of the study's results with regard to ETS, although they support an increase in lung cancer risk with spousal smoking.

A.10. GARF (Case-Control)

A.10.1. Author's Abstract

"In a case-control study in four hospitals from 1971 to 1981, 134 cases of lung cancer and 402 cases of colon-rectum cancer (the controls) were identified in nonsmoking women. All cases and controls were confirmed by histologic review of slides, and nonsmoking status and exposures were verified by interview. Odds ratios (OR) increased with increasing number of cigarettes smoked by the husband, particularly for cigarettes smoked at home. The OR for women whose husbands smoked 20 or more cigarettes at home was 2.11 (95% C.I. 1.13, 3.95). A logistic regression analysis showed a significant positive trend of increasing risk with increasing exposure to the husband's smoking at home, controlled for age, hospital, socioeconomic class, and year of diagnosis. Comparison of women classified by number of hours exposed a day to smoke in the last five years and in the last 25 years showed no increase in risk of lung cancer."

A.10.2. Study Description

This study was undertaken in New Jersey and Ohio to investigate the relationship of involuntary smoking to primary lung cancer. All data were collected specifically for this study, and only nonsmokers were included as subjects. Cases are the lifelong nonsmoking women histologically diagnosed with primary lung cancer during 1971-81 in four participating New Jersey and Ohio hospitals. Controls selected from patients with colorectal cancer were matched 3 to 1 to a case on hospital and age (± 5 years). Subjects were not restricted to incident cases, and controls were apparently cumulatively sampled. Exposure data were obtained by blinded, face-to-face interviews with subjects or their relatives.

A total of 1,175 female lung cancer cases were initially identified from medical records. Exclusion of women found to be current or former smokers or not to have histologically verified primary lung cancer eliminated 1,041 of the identified cases, leaving 134 ETS subjects. Interviews were conducted with patient, spouse, or child in about 75% of the subject population, whereas the rest were conducted with another relative. The age distributions of cases and controls are nearly identical.

ETS exposure includes pipe and cigar use as well as cigarette smoking. Three sources of passive smoking are considered, which will be referred to as follows: "exposure to husband's smoke" means having a husband *or* other related cohabitant who smokes more than occasionally, either (1) anyplace or (2) at home; "general exposure" applies to the smoke of others at home, work, or otherwise who have smoked more than occasionally during the past (1) 5 years or (2) 25 years; and "childhood exposure" refers to experiencing ETS from any source during childhood. Husband's smoking is quantitated as cigarettes per day and years smoked; general exposure is given as average hours per day; and childhood exposure is treated as a dichotomous variable. Only 57 percent of the cases were women living with a husband at the time of diagnosis. No checks on exposure status are described, and no classification of subjects by marital status was implemented. Adenocarcinoma (87) predominates among lung cancer cases, followed by large cell (21), small cell and miscellaneous (15), and squamous cell cancer (11); no data on airway proximity are provided.

Ninety of 134 cases were exposed to husband's (or other relatives') smoking at home, compared to 245 of 402 controls, giving a crude odds ratio of 1.31 (reported 95% C.I. = 0.99-1.73; C.I. calculated by reviewers is 0.87-1.98). For husband's smoking of 20 or more cigarettes per day, the highest exposure category, the odds ratio increases to 2.11 (1.13-3.95). Husband's smoking averaged 11.5 cigarettes per day for the exposed subject. For husband's smoking anyplace, 91 of 134 cases and 254 of 402 controls were exposed, giving a crude odds ratio of 1.23 (0.94-1.60). At the highest exposure category, 40 or more cigarettes per day, the odds ratio is 1.99

(1.13-3.50). Cigar and pipe smoking alone yields odds ratios of 1.17 and 1.13 for husband's smoking at home and anyplace, respectively. There are statistically significant trends for both husband's smoking at home and for smoking anyplace when measured by cigarettes per day, but not when evaluated by number of years smoked. The odds ratio for ETS exposure from husband's smoke, both total and at home, is calculated by source of interview respondent for the categories of "self," "husband," "daughter or son," and "other." It is readily apparent that the excess risk is attributable to "daughter or son," with some contribution from "other." *None* of the excess risk is attributable to "self" or "husband."

General smoke exposure also shows an association with lung cancer. Exposure over the past 5 and past 25 years yield odds ratios of 1.28 (0.96-1.70) and 1.13 (0.60-2.14), respectively. The odds ratios do not increase with increasing level of exposure, however, and none of the associations is statistically significant. No association was found between childhood smoke exposure and lung cancer (OR = 0.9, 0.74-1.12). When the odds ratio is calculated by source of respondent, "other" and "self" account for the excess risk when smoking for 5 years is the measure; for 25 years of smoking, "other" and "daughter or son" account for the excess risk.

Stratification by cell type reveals that husband's smoking is much more strongly associated with squamous cell (OR = 5.00, both for smoking at home and anyplace) than adenocarcinoma (corresponding ORs = 1.33 and 1.48); no association with other cell types was detected. Stratification by age and socioeconomic status suggests little effect of these variables on the results. The results, however, appear to be sensitive to whether the interview data were obtained from the subject or a surrogate (offspring, relative, etc.), as noted above.

A logistic regression analysis including adjustment for age, hospital, socioeconomic status, and year of diagnosis was undertaken for passive smoking. Cigarettes per day of husband's at-home smoking is significantly associated with lung cancer, with an estimated relative risk of 1.7 at exposure of 20 cigarettes per day compared to none. In contrast, husband's smoking outside the home is *not* significantly associated with lung cancer, although the estimated relative risk is 1.26 for 20 cigarettes per day. General smoke exposure is not significantly associated with lung cancer, for either the 5 years or past 25 years of exposure. Adjustment for type of respondent reportedly had no significant effect on the logistic regression results.

A.10.3. Comments

The abundance of nonsmoking cases (134) and controls (402) in this study relative to most ETS studies gives it above-average statistical power. Comparability of cases and controls appears good based on their very similar age distributions, matching on hospital and age, and restriction to

nonsmokers. But the lack of further demographic comparisons means that divergence on some other factor(s) cannot be ruled out.

A major difficulty in this study, however, arises from the extensive use of proxy respondents. Only 12% (16 of 134) of the case interviews were with the patient. In the stratified analysis, it was found that the husband's smoking at home is positively associated with lung cancer only when the smoking information is provided by a son or a daughter rather than by the patient or her husband. This leads to two possibilities. Either the son or daughter claimed that the patient's husband smoked when he actually did not, thereby shifting cases from the nonexposed to exposed category and increasing the odds ratio, or the patient or her husband claimed that the husband did not smoke when actually he did, thereby shifting cases from the exposed to nonexposed category and depressing the odds ratio. In general it is thought more likely that true smokers are misclassified as nonsmokers more often than true nonsmokers are misclassified as smokers (see, for example, Lee, 1986, and Machlin et al., 1989). Also, Machlin indicates that proxies tend to misclassify smokers no more often than smokers themselves do. Thus, it may be that the son or daughter data are better than the self or husband data. On the other hand, the difference among the reporting sources may be due only to chance because the results in JANE on self or proxy reports are quite the opposite of those in this paper, with the proxy reports (in this case including the spouse) leading to lower odds ratios than the self-reports.

Another possible problem with this study is the use of colon and rectal cancer cases as controls on the theory that these diseases are not smoking related. A recent paper, Zahm (1991), notes that associations have been found between smoking and these cancers. If these associations carry over to passive smoking, they might bias the result either higher or lower.

In general, the detailed results from the stratified analysis in Table 6 of the paper exhibit considerable variation, probably caused by chance. Hence, the overall results in Table 5 of the article, where all the cases and controls are used, may be the most reliable. They indicate an odds ratio of 1.31 (1.24 after adjustment for smoker misclassification bias in the body of this report) for exposure to all types of husband's smoking at home.

The study's exposure assessment methodology is strengthened by the attempt to maintain blinding by not informing interviewers of the study hypothesis or the subjects' disease status. This is impractical in most studies, but given the use of controls who also have cancer and a high proportion of proxy interviews, effective blinding of interviewers *and* subjects may have been largely achieved here. Detailed data on smoke exposure at home as well as elsewhere, including pipe and cigar smoking, were collected. Pipe and cigar smoking are often not considered in ETS studies, thus constituting a potential source of exposure misclassification, and smoking at home

should be a more meaningful index of smoke exposure than total smoking. What the authors termed "husband's smoking" actually includes smoking by related cohabitants as well. Presumably this was done both to increase subject numbers (by not excluding unmarried women) and to enhance detection of passive smoke exposure. However, it could cause some oversight with regard to classification of ETS exposure (e.g., a widow, living with a nonsmoking sister, whose husband had been a heavy smoker). Less understandable is the failure to include smoking by *un*related cohabitants and the inclusion of single women living alone. Diagnostic misclassification is unlikely given the histological verification of all cases *and* controls.

Both husband's at-home and total cohabitant smoking are associated with lung cancer, the association being stronger for at-home smoking. Both exposures show a statistically significant general increase in association with level of smoking, with substantial associations only at high levels. The adjusted association for at-home cohabitant smoking is much stronger (OR = 1.7; $p = 0.03$) than that for smoking outside the home (OR = 1.3; $p = 0.13$), a pattern consistent with home smoke exposure rather than some other smoking-related factor as the basis of the observed results. General ETS exposure, in contrast, was inconsistently related to lung cancer in the unadjusted analyses, with a stronger association for exposure within the last 5 years than within the last 25 (possibly attributable to better recall). No dose-response pattern is evident, however, and no association was found in the adjusted analyses.

The adjusted analyses include age, hospital, socioeconomic status, and year of diagnosis in a logistic regression model, along with the passive smoking variable. This adjustment did not significantly reduce the association between husband's smoking at home and lung cancer observed before the adjustment, but it did eliminate any association with general ETS exposure. Thus, the results for husband's smoking at home are probably not attributable to confounding by age, socioeconomic status, hospital, or temporal variables. Dietary factors, heating and cooking practices, and family history of cancer were not considered as potential confounders; thus, an effect by one or more of these factors cannot be ruled out.

The heavy reliance on proxy respondents and their uncertain impact on the analysis leaves some uncertainty to interpretation. On the favorable side of this issue, the authors' attempt to blind subjects and interviewers to the study hypothesis lessens the likelihood of potential bias from proxy response, and no effect due to respondent type was found in the adjusted analyses. Some of the exposure categories seem vague, but this would tend to reduce the magnitude of the observed association rather than to give rise to one. In summary, this study is suggestive of a dose-dependent association between smoking in the home and lung cancer, with reservations due to the use of proxies.

A.11. GARF(Coh)

A.11.1. Author's Abstract

"Lung cancer mortality rates were computed for nonsmokers in the American Cancer Society's prospective study for three 4-year periods from 1960 to 1972 and in the Dorn study of veterans for three 5-year periods from 1954 to 1969. There was no evidence of any trend in these rates by 5-year age groups or for the total groups. No time trend was observed in nonsmokers for cancers of other selected sites except for a decrease in cancer of the uterus. Compared to nonsmoking women married to nonsmoking husbands, nonsmokers married to smoking husbands showed very little, if any, increased risk of lung cancer."

A.11.2. Study Description

This study examines the role of passive smoking in lung cancer among married women in the United States. It uses data collected in a large prospective study initiated by Cuyler Hammond of the American Cancer Society (ACS) in 1959. The ACS's objective was to evaluate the association between potential cancer risk factors and cancer mortality. Although data were collected on the smoking status of women and their spouses at the start of the study, Hammond thought the study data should not be used to estimate lung cancer death rates in relation to amount of passive smoking by female never-smokers. Specifically, Hammond notes that the study was not designed for that purpose, and no special information on the subject was obtained; information was available on the smoking habits of the husbands of many of the married women in the study, but not on the smoking habits of the former husbands of women who were widowed, divorced, separated, or married for a second time. More important is his statement that women in America at that time were not generally barred from public and social gatherings where men were smoking, and working husbands who smoked generally did much if not most of their smoking away from home (Hammond and Selikoff, 1981). Similar reservations are expressed by Garfinkel, who also notes that 13% of the women nonsmokers who died of lung cancer in the ACS study reported that they were previously married and that the classification of their exposure to their husbands' smoking may not be pertinent (Garfinkel, 1981, p. 1,065).

A total of 29 ACS divisions encompassing 25 states took part in the study; participating counties were in turn selected by division leaders based on feasibility. Data collection was undertaken by networks of volunteers set up within participating counties. Recruitment of subjects and subsequent follow-up monitoring were undertaken by volunteers who were instructed to enlist qualifying acquaintances. Subjects were restricted to persons more than 30 years of age whose household contained at least one person over 45 years of age. Illegal

immigrants and persons who were illiterate, institutionalized, or itinerant were excluded. Detailed questionnaires were distributed to subjects and all members of their household over 35 years of age. These questionnaires covered factors such as diet, alcohol consumption, and occupational exposures as well as smoking habits, but they did *not* address passive smoke exposure. Volunteers who recruited subjects were given responsibility for tracing the subject's vital statistics for the next 6 years and contacting living subjects again in 1961, 1963, and 1965 to complete a questionnaire on changes in smoking habits. Alternate researchers were appointed as necessary to replace volunteers who moved or quit. Finally, death certificates were obtained for subjects reported deceased; where death due to cancer was indicated, verification was sought from the certifying physician. Although follow-up initially ceased with 1965, in 1972 an additional follow-up was initiated in 26 of the original 29 ACS divisions and terminated in September 1972.

A.11.3. Comments

The passive smoking study being described (GARF[Coh]) was undertaken by assembling a subcohort of married women who reported that they had never smoked and whose husbands completed a questionnaire including smoking habits. This subcohort totaled 176,739 women out of the 375,000 never-smoking women enlisted by the ACS in 1959. Women were divided into three exposure categories based on their husband's smoking status—nonexposed for never-smokers, and low (high) for current smokers of less (more) than 20. Wives of former cigarette smokers and men who smoked cigars or pipes rather than cigarettes were excluded (Garfinkel, 1984); presumably these had already been excluded from the reported total (176,739). Mortality rates were computed by 5-year age intervals for unexposed women (i.e., wives of nonsmokers), from which the expected number of deaths for exposed women was estimated under the hypothesis that spousal smoking does not affect lung cancer mortality. The ratio of observed to expected deaths in the exposed group provides an age-standardized mortality ratio. This mortality ratio is 1.27 (95% C.I. = 0.85-1.89) for spousal smoking of under 20 cigarettes per day (low exposure) and 1.10 (0.77-1.61) for over 20 cigarettes per day (high exposure).

In a separate analysis, women healthy at the start of follow-up were divided into groups matched on age (5-year grouping), race, education, urban or rural residence, and occupational exposure of husband to dust, fumes, or vapors. Each of these matched groups was then subdivided into zero, low, and high exposure categories. The proportion of observed deaths in each category was multiplied by the proportion of subjects in the smallest category of the matched group relative to that category. This "adjusted" number of deaths was then summed across all groups with a given exposure and compared with the corresponding value for the unexposed (zero

exposure) category to provide a mortality ratio. In addition, we conducted a Mantel-Haenszel analysis of mortality using data supplied by Garfinkel that yielded results similar to the author's analyses. Ages 35 to 39 and 70 to 79 were excluded due to insufficient numbers. After stratifying by age and correcting for time under study, the calculated lung cancer risk was greater in subjects whose husbands smoked, but the predicted risk at low exposure was greater than at high exposure. It is notable, however, that the lower risk at higher exposure is entirely attributable to the 50- to 59-year-old age group; otherwise, predicted mortality would be equivalent at the low and high exposure (see Table C-1 of this report).

The original ACS cohort study was a massive undertaking. By using it as the basis of his cohort, Garfinkel was able to assemble a very large number (over 170,000) of never-smoking married women. A cohort of this magnitude attains a number of lung cancer cases ordinarily feasible only by means of a large case-control study, while avoiding the attendant pitfalls of potential recall and interviewer bias associated with case-control studies. There are several important limitations, however, that make the results of this study difficult to interpret.

The ACS study was not designed to yield a representative sample of the general population. The sample of women is older (all at least 35 years of age, two-thirds between 40 and 59 at start of follow-up), more educated (only 5.6% were limited to a grade school education), and contains a much smaller proportion of ethnic minorities (only 6.8% nonwhite) than the general population (Stellman and Garfinkel, 1986). Although not representative of the population as a whole, the relative homogeneity of the subject population does reduce the potential for complications of interpretation that differences in ethnic or socioeconomic factors or both may pose, and it increases efficiency by not including subjects belonging to age groups unlikely to experience significant mortality during follow-up. Overall, the study population's unrepresentativeness strengthens rather than undermines the study's conclusions. It would have been useful, however, to confirm that exclusion of greatly underrepresented groups, such as nonwhites and persons with no formal education beyond the eighth grade, had no effect on the results.

Because the data on smoking habits were collected prospectively, no information on exposures prior to 1959 was obtained. Exposure history for the years before 1959 may be as important as for the 12 years of follow-up, however, if lung cancer has a long latency period, such as 20 years or so. Inclusion of persons whose exposure status may have changed markedly by 1959 could be a biasing influence. Neither were changes in exposure status during the follow-up period considered, despite the availability of data on smoking habits in 1961, 1963, 1965, and 1972. In fairness to the author, keep in mind that our comments are directed at evaluation of the

study for its contribution to the issues of passive smoking and lung cancer, although the ACS study was not designed to assess ETS exposure. The only data collected on ETS exposure are based on the spouse's *current* smoking habits at initiation of the study. If the ACS study had been directed at evaluation of health effects of ETS, these issues would likely have been taken into consideration to sharpen the classification of subjects with respect to ETS exposure. Overall, the likely consequence of these factors is to reduce the sensitivity of the study to detect an association between lung cancer and ETS exposure, but the potential for bias in the direction of a false positive cannot be ruled out. For example, if wives of smokers are more likely to become active smokers during follow-up than wives of nonsmokers, these changes in smoking status could bias results toward finding a positive association with passive smoking. (Relevant to this particular example, the authors state that "very few" subjects reported a change in their smoking status, but provide no further details. Also, 12 or fewer years is a short exposure to produce lung cancer. It is thus probable that any bias introduced by active smoking would be minor; furthermore, the fact that a stronger association was observed for low than for high levels of spousal smoking argues against a confounder associated with spousal smoking. Nevertheless, potential sources of bias may be present that influence the study outcome in either direction.)

During 1959-65, confirmation of primary lung cancer diagnosis was obtained from physicians for 78% of all cancer cases. Among 203 cases of lung cancer in nonsmoking women diagnosed by death certificate, confirmation attempts on an unspecified number of these cases found 34 misdiagnosed as primary lung cancer, whereas 10 primary lung cancers were discovered among cancers diagnosed as nonlung on death certificates. Thus, it appears that only about 85% of the death certificate diagnoses of primary lung cancer were accurate, while a small percentage of primaries were misdiagnosed as cancers of other cites. No confirmation of diagnoses was undertaken during the period after 1965 when nearly two-thirds (119 out of 182, according to data supplied to reviewers by Garfinkel) of the lung cancer deaths in the ETS study population were reported. In light of the misdiagnosis rates found for 1959-65, it is likely that a substantial percentage of the study's reported primary lung cancers in cases actually arose in other sites, whereas a substantial percentage of reported cancers of other sites actually arose in the lung. The resultant errors in subject classification probably bias the results toward no association (i.e., a false negative conclusion), *if* a positive association actually exists.

Loss of subjects to follow-up is another source of potential bias. A subsequent report on the ACS cohort (Garfinkel, 1985) states that, whereas more than 98% of the original cohort was successfully traced through 1965, over 10% (3 of 29) of the original ACS divisions declined to participate in the 1971-72 follow-up effort. In the study now under review, Garfinkel reports

successful follow-up of 98.4% through 1965 and 92.8% through 1972, apparently not considering subjects in the division who declined to participate in the extended follow-up as losses. It thus appears that, whereas more than 98% of the original cohort was successfully followed up through 1965, less than 90% of the cohort was targeted for follow-up through 1972, and losses for this targeted group approached 7%. Such losses not only reduced the number of observed deaths—and, hence, the study's power—but introduced the possibility that differential loss to follow-up could have distorted the study's results. A greater proportion of losses among exposed subjects than among unexposed could partially mask a true positive association, whereas greater loss among the unexposed could potentially create a spurious association.

Aside from the issues above, the study controls for basic sources of potential confounding. Subjects were all of the same gender and marital status, and age was controlled for in all analyses. Analysis by groups matched on race, education, residence, and occupation, along with age, produced nearly identical results as the analyses standardized by age alone, indicating no confounding due to these and unlikely confounding due to other socioeconomic, occupational, or geographic factors.

In summary, this study predicts a weak positive association between spousal smoking at levels of 1 to 19 cigarettes per day and lung cancer, but only slight association at higher exposure levels; neither association is statistically significant. The lack of apparent dose-response pattern further undermines the association, but the confidence intervals of the point estimates for the high and low exposure groups overlap so broadly that the existence of a dose-response relationship cannot be ruled out entirely. Meaningful interpretation of the results for the issue of ETS exposure and lung cancer, however, is limited. As the study's objectives were directed elsewhere, the data collected on ETS exposure is limited to the status of spousal smoking at the start of the study. Past history and future changes in status are not well addressed. There is ample indication that death certificate diagnoses are not a reliable source for the selection and classification of subjects. Although a second 6-year follow-up period was undertaken to increase the follow-up period to 12 years, its success was limited by incomplete participation and, perhaps, by organizational difficulties related to long-term reliance on volunteers (who may relocate, change interests, lose contact with the subjects originally enlisted over an extended period, etc.). Even if the follow-up were entirely successful, however, 12 years of follow-up without regard to exposure experience is not a particularly long period to evaluate the lung cancer potential for ETS because the latency period associated with active smoking may be on the order of 20 years. Although the ACS study has been an important contribution to its main study objectives,

the lack of information and potential sources of bias for the issue of passive smoking and lung cancer leave its assessment in question.

A.12. GENG

A.12.1. Author's Abstract

Not included in source.

A.12.2. Study Description

This study was conducted in Tianjin, where China's highest incidence of female lung cancer occurs, to illustrate the relationship between cigarette smoking and female lung cancer. The study explores both active and passive smoking, so the analyses for passive smoking apply to a subgroup of the larger subject population. The source of the study's subjects and the time over which they accrued is not specified. Subjects resided in Tianjin for over 10 years. The source of controls is not given, but they consist of females pair-matched with cases on race, age (± 2 years), marital status, and birthplace. It is unclear from the article whether cases were incident or prevalent and how controls were obtained. A draft summary description of this study (Liang and Geng, undated) from Liang indicates, however, that hospitalized cases (96) were matched with inpatient controls and general population cases (61) were matched with neighborhood controls.

The source of the study's exposure data is not clearly stated, but the draft from Liang indicates that all identified cases and controls were interviewed. No information on collection or verification of smoking or other data is provided. The authors state that cases and controls do not differ significantly in age, education, occupation, race, marital status, birthplace, or residence, but this refers only to the total study population of 157 cases and 157 controls that includes active smokers; the same similarity may not hold for the 54 cases and 93 controls used in the passive smoking analysis. Tumor types are provided for 85% of the total case population, but not specifically for the passive smoking subpopulation; adenocarcinomas (36.9%) predominate, being about twice as common as squamous (22.3%) or small cell (19.7%) tumors. Although nearly 85% of the total cases were diagnosed histologically or cytologically, it does not appear that verification of diagnosis or primary status of tumor was undertaken by the authors, and no information on tumor distribution is supplied.

A nonsmoker (which usually means never-smoker) is ETS exposed if the spouse smokes. Presumably women not currently married are excluded from the analysis, although they could have been included with some assumption made regarding their exposure status. Information on dose and duration of exposure was collected but not used in the passive smoking analysis, and it is

not indicated if cigar or pipe smoke was included. ETS exposure from parents and colleagues is reported to have been evaluated. The parental smoking referred to is apparently in adulthood, as cohabitants in the home, but that is not made explicit. Exposure during childhood was not specifically addressed.

Among the ETS subjects, 34 out of 54 cases and 41 out of 93 controls were exposed. This yields a statistically significant crude odds ratio of 2.16 (95% C.I. = 1.03-4.53) for husband's smoking. No analyses adjusted for age or other factors are reported. On a rather confusing note, an odds ratio of 1.86 is cited twice later, but that value is inconsistent with the odds ratio of 2.16 from the raw data. Whether this is an error or the product of an unspecified adjustment by conditional logistic regression, which the authors employ for other purposes throughout the paper, is unknown. The odds ratio increases with the number of cigarettes smoked per day by the husband and with the duration of the husband's smoking. The odds ratios for smoking rates of 1 to 9, 10 to 19, and 20 or more cigarettes per day are 1.4, 2.0, and 2.8, respectively. For 1 to 29, 20 to 39, and 40 or more years of exposure, the odds ratios are 1.5, 2.2, and 3.3, respectively. No tests for trend are cited, and the relevant data are not given. Consideration of ETS exposure from smoking by father, mother, or "colleagues" reportedly yielded no results that are "quite significant." No further details are provided, and it is not clear whether these results consider past smoking status or apply only to current status.

The authors conclude that active and passive smoking are the most important risk factors for female lung cancer in Tianjin. They attribute 35% to 42% of lung cancer occurring in their nonsmoking female population to passive smoking. Female lung cancer is also found to be associated with other factors, such as occupational exposure, with an odds ratio of 3.1 (95% C.I. = 1.58-6.02); history of lung disease, with an odds ratio of 2.12 (95% C.I. = 1.23-3.63); and cooking with coal, where the odds ratio increases with the duration of exposure from 1.5 to 5.5 (see Table 8 of this reference).

A.12.3. Comments

The quality of this study is difficult to assess given the dearth of details supplied by the authors. Certainly the number of nonsmoking cases and controls included is more substantial than in some other studies, and the reported association between passive smoking and lung cancer is statistically significant. Questions regarding the mechanics of data collection and analysis, however, remain unanswered.

Exposure and other data were obtained from hospitalized subjects at bedside and from others in their homes. The extent (if any) to which information was obtained from proxy

responses, or interviews were denied, is unspecified. No blinding was employed, but that may have not been feasible. Despite the reported similarity of the demographic characteristics of the total case and control populations, dissimilarity cannot be ruled out within the subgroup used for ETS analyses. Although the whole study, including active smokers, is matched on several variables, the matching need not apply to the ETS subjects alone.

Lack of validation of diagnostic and exposure information may have led to substantial misclassification, although the fact that 85% of the lung cancer diagnoses were obtained via histology or cytology suggests that diagnostic misclassification would not have been extreme. Lack of consideration of former smoking status is a potential problem. Inclusion of former smokers among the nonsmokers, in combination with a tendency for former smokers to marry smokers, could produce an upward bias in the odds ratios.

Finally, although the crude odds ratio of 2.16 for passive smoking is statistically significant, it does not take into account even the most basic potential confounder—age. For the larger case-control population (including smokers), occupational exposure (OR = 3.1), history of lung disease (OR = 2.64), and cooking with coal (OR = 1.54-5.56, rising with cumulative exposure) are statistically significant risk factors that the authors claim have joint effects with smoking, yet the ETS analysis is not adjusted for these likely confounders. The anomalous odds ratio of 1.86 given later in the results *may* have been adjusted for age or other factors, but there is no way to tell.

In summary, the study's results are consistent with the hypothesis that passive smoking increases the risk of lung cancer, but they are not definitive. More detail regarding the mechanics of the study is needed to assess its general validity. If warranted, a clearer and more complete analysis of the study's data regarding passive smoking, including consideration of the information on dose, duration, and potential confounders already available, would then be useful. For the current evaluation of epidemiologic evidence on ETS exposure and lung cancer, too many questions remain about the design and execution of the study to properly interpret the data and assess the authors' conclusions.

A.13. HIRA(Coh)

(*Note:* Because of the many publications relating to this study, a different format of presentation is used.)

This cohort study and a later case-control study based on it were undertaken to explore the relationship of passive smoking and other factors with lung cancer in Japanese women. Subjects

and data used in this study were, however, drawn from a larger study that was not designed to investigate passive smoking.

An exploratory study of mortality determinants targeting adults at least 40 years of age inhabitating 29 health center districts in Japan was initiated in 1965. In autumn of 1965, more than 90% of the target population was interviewed to ascertain the status of lifestyle factors that might affect health (e.g., cigarette smoking, alcohol consumption, and occupation). Individuals, including husbands and wives, were interviewed separately. Follow-up of the interviewees was conducted using a combination of an annual census of residents and death certificates to monitor mortality. Mortality, as determined by death certificate, was the outcome variable. Hirayama used this study population to examine the potential effect of passive smoking on lung cancer mortality. In 1981, he reported the results derived from the first 14 years of follow-up (through 1979) in the *British Medical Journal.*

A total of 142,857 women were interviewed in 1965, of whom 91,540 were nonsmokers whose husbands had also been interviewed regarding smoking status. Using their husbands' smoking status as a surrogate for exposure to ETS, Hirayama calculated lung cancer mortality rates for comparison of women married to smokers with women married to nonsmokers; rates were also calculated using various strata of spousal smoking intensity (number of cig./day), as well as age and occupation. A total of 346 lung cancer deaths occurred in this cohort during the first 14 years of follow-up.

After standardization for age and occupation, it was found that women whose husbands smoked daily had a higher annual rate of lung cancer mortality than did women whose husbands were nonsmokers or only "occasional" smokers. The rate increased with the level of smoking (e.g., 8.7/100,000 annually for no or occasional smoking, 14.0 for smoking 1-19 cig./day, and 18.1 for 20+ cig./day). Higher rates and a dose-response pattern were observed in women married to smokers after stratification on either husband's age or agricultural work status. Mortality due to two diseases associated with active smoking, emphysema and asthma, was also higher in wives of smokers and increased with exposure. Conversely, mortality due to two cancers not linked to active smoking, cervical and stomach cancer, was no higher in wives of smokers. Consideration of husbands' drinking habits had no significant impact on mortality for lung cancer or other diseases mentioned above.

Further study results appeared in the October 3, 1981, issue of *British Medical Journal.* Among other things, results were presented by husband's age in 10- instead of 20-year intervals and for 10 occupational categories instead of 2. These tabulations revealed a statistically significant overall association between husbands' smoking and lung cancer mortality with a dose-

response pattern (1.00 RR for nonsmokers plus former smokers, 1.44 RR for medium smokers, and 1.85 RR for heavy smokers). Also of interest was a breakdown of lung cancer mortality and smoking habits in greater detail for both husband and wife. Notably, nonsmoking *husbands* with smoking wives showed a higher lung cancer mortality rate (RR = 2.94) than did those with nonsmoking wives. Because nonsmoking husbands with smoking wives were rather rare, however, the numbers in this stratum were low (only seven deaths); thus, the observed association was not statistically significant.

In 1984, Hirayama published results of an additional 2 years of follow-up of his cohort in *Preventive Medicine*. The same basic associations reported after 14 years of follow-up for spousal smoking and lung cancer remained after 2 additional years of follow-up. Mortality rates increased with increasing exposure after stratification by age of husband, occupation, geographical area, and time period during study; a trend had been reported after stratification for age of wife at start of study only for ages 40 to 49 and 50 to 59. It was also reported that the elevation of lung cancer mortality in nonsmoking women married to smokers was significantly less among women who consumed green-yellow vegetables daily (e.g., for spousal smoking of 20+ cig./day, the RRs for disease mortality were 1.63 and 2.38). No such pattern was observed for ischemic heart disease. In addition, a statistically significant excess of para nasal sinus cancer in nonsmoking wives of smokers had been observed, which showed an apparent dose-response relationship across four smoking categories, culminating in an RR of 3.44 for spouses of smokers of more than 20 cigarettes per day. That effect dwarfed those related to social class and dietary factors that were also examined.

In 1988 Hirayama reported the results of a case-control study nested within his cohort in *Environmental Technology Letters*. To explore the relationship of women's age at marriage, as well as husbands' smoking status with lung cancer mortality, lung cancer cases occurring among nonsmoking women in the cohort study were contrasted with stomach cancer cases as controls. Including only women under 59 years of age at the start of the cohort, the study divided husbands' smoking into three categories—none, 1 to 19, and 20 or more cigarettes per day. Age at marriage was also trifurcated in 19 or fewer, 20 to 23, and 24 or more years. Apparently as a result of exclusion of women over the age limit or because of missing data, only 115 cases and 423 controls were ultimately compared out of the 200 lung cancers and 854 stomach cancers among the nonsmoking female cohort. Adjusting for woman's age and husband's smoking category resulted in odds ratios for lung cancer of 4.95, 1.76, and 1.41 for the respective age-at-marriage groups; the first two of these odds ratios were statistically significant. An additional comparison found

that among lung cancer cases, the mean age at first marriage to a smoking husband was nearly 8 years less than the mean age at start of smoking for active smokers.

A greatly expanded nested study was presented in the following year (Hirayama, 1989). The study was designed to explore the potential for confounding of the relationship between lung cancer and spousal smoking by dietary habits. A "baseline" sample of 2,000 nonsmoking wives with known spousal smoking habits, aged 40 to 69 at the start of the cohort study, was randomly selected from the available cohort of 90,458 for comparison with the 194 lung cancer cases occurring in equivalent subjects within the cohort. After determining that the age distributions of the case and baseline groups were very similar within smoking categories, the combined population was stratified on daily versus less-than-daily consumption for each of five food types (green-yellow vegetables, fish, meat, milk, and soybean paste soup) and wives with smoking and nonsmoking husbands were contrasted to assess differences in dietary habits. After adjustment for wife's age and husband's occupation, only daily meat consumption was significantly more common among wives of smoking husbands, and this was limited to smokers of 20 or more cigarettes per day. Calculation of odds ratios for dietary habits resulted in a "significant" elevation only in daily fish consumers (OR = 1.365, 90% C.I. = 1.05-1.77; Table IV). A nearly significant *lowering* of the odds ratio was found in daily meat consumers.

Finally, odds ratios were calculated for lung cancer adjusted by wife's age, husband's occupation, and each of the dietary habit categories in succession. A dose-response pattern was observed between lung cancer and husband's smoking that persisted after adjustment for any of the five dietary factors. Odds ratios for the five dietary habit categories ranged from 1.42 to 1.69 for former smokers and smokers of 1 to 19 cigarettes per day, and from 1.66 to 1.91 for smokers of 20 or more cigarettes per day compared with nonsmoking husbands. The observed trend was highly statistically significant, regardless of which factor was adjusted for in the calculation.

A.13.1. Chronology of Controversy

Publication of Hirayama's initial 14-year follow-up results in 1981 provoked a sizeable volume of commentary in the scientific literature. Following the release of updated results in 1983-84, the study attracted little controversy until the latter part of the 1980's, when criticisms were directed at the study by a number of authors. This process reached its culmination in response to the EPA's release for external review of the document *Health Effects of Passive Smoking: Assessment of Lung Cancer in Adults and Respiratory Disorders in Children*, which placed considerable emphasis on Hirayama's results. An author-by-author, letter-by-letter consideration of the arguments regarding Hirayama's work would be dauntingly duplicative and

tedious. Instead, the most-discussed concerns will be highlighted, followed by an overall assessment of the study as it stands today.

Chronology of Selected Events Relevant to the Hirayama Cohort Study

Jan. 7, 1981	Results of cohort study are published in *British Medical Journal* (282:183-185).
Oct. 3, 1981	Comments and letters to the editor by Kornegay and Kastenbaum (of the U.S. Tobacco Institute), Mantel, Harris, and DuMouchel, and MacDonald appear re: Jan. 7 article in *British Medical Journal*, along with the author's reply.
March 3-5 & July 10-15, 1983	Hirayama presents updated results for his study cohort incorporating an additional 2 years of follow-up (for a total of 16 years) to the International Lung Cancer Update Conference in New Orleans and the 5th World Conference on Smoking and Health in Winnipeg, Canada.
Dec. 17, 1983	Updated results of the cohort study are published in *Lancet*.
1984	Results presented in conference of July 1983, and in summary form in *Lancet* later that year, are published in full in *Preventive Medicine*. In addition, Hirayama now reports a statistically significant increase in brain tumors with husbands' smoking. In a round-table discussion published in the same journal, Lee proposes that misclassification of active smoking status may have biased Hirayama's results.
1985	Another publication of results for the 16-year follow-up appears in *Tokai Journal of Experimental Clinical Medicine*.
1987	Hirayama includes previously published study data in a book chapter (Aoki et al., 1987).
1988	Uberla and Ahlborn publish an article from the *Proceedings of the Indoor Ambient Air Quality Conference* in London (which is essentially the same as an earlier presentation at the 1987 Tokyo International Conference on Indoor Air Quality) criticizing the Hirayama study on several grounds. Their primary assertion is that correction for the cohort's age distribution removes the apparent effect of spousal smoking.
1988	Hirayama publishes the results of nested case-control study based on cohort study data in *Environmental Toxicology Letters*. Estimated risk of lung cancer is reported to increase with earlier age of marriage to smoker.
1989	Layard and Viren publish a paper presented at the Conference on the Present and Future of Indoor Air Quality in Belgium. Making their own projections of expected deaths and estimating losses to follow-up, they conclude that mortality rates were anomalously low and follow-up losses unacceptably high in the Hirayama study.

1989 Hirayama publishes nested case-control results in *Present and Future of Indoor Air Quality*. Positive association of husband's smoking and lung cancer with dose-response pattern reported after adjustment for dietary variables.

A.13.2. Some Major Critical Works

A basic point raised by MacDonald (1981) and others soon after publication of Hirayama's initial results concerns the selection of the study's sample population. It appears that the 29 health centers included in the study were selected on grounds of convenience rather than to provide a randomly sampled, representative cross-section of the Japanese population. The resultant sample may thus be unrepresentative of the Japanese population as a whole.

A convenience sample may still produce a fairly good cross-section of the population, and Hirayama replied in 1981 that "the satisfactory representativeness [of the study population] . . . with regard to demographic and social indices was confirmed after the survey." He did not, however, provide supporting data. MacDonald (1981) contends that the six prefectures from which the sample was drawn are relatively industry-heavy (which does not necessarily contradict Hirayama's contention); data presented by Hirayama (1983) showed that 40,390 of the cohort's wives were married to agricultural workers, 19,264 to industry workers, and 31,886 to "others," which would indicate some overrepresentation of agricultural areas. Women aged 70 or more are clearly underrepresented, composing less than 1% of the study's 40-and-older nonsmoking female population. Thus, the cohort may be unrepresentative to some degree, but *how* unrepresentative is unclear.

The key problem arising from an unrepresentative sample is that it may limit generalizability of results derived from that sample to the population as a whole. In lieu of good reasons to think that the association between exposure and disease would be different in the study population and the general population, however, the possibility of an unrepresentative sample assumes less importance. And, as will be seen in the subsequent discussion of possible confounders, similar patterns of association were observed in a number of demographic sub-groups.

Misclassification may occur in any epidemiologic study. Most of the critical commentary has focused on potential misclassification of exposure status. Because the study relies on interview data to establish smoking status, misreporting by interviewees may affect accurate classification of both wives *and* their husbands' smoking habits. It has been argued that women are especially likely to misrepresent their smoking habits because smoking is considered less socially acceptable for women than for men, particularly in Asian societies. Such misclassification

would tend to reduce the degree of association between passive smoke exposure and its effect(s) if women in the "exposed" and "unexposed" groups were equally likely to misreport their own smoking. One of the most prominent criticisms leveled at the Hirayama study postulates a differential misclassification of smoking status in women. Peter Lee (Lehnert, 1984) raised the argument that if women married to smokers are more likely to be (or to have been) smokers than are women married to nonsmokers, and a given percentage of smoking women claim to be nonsmokers, then purportedly nonsmoking wives of spousal smokers will include a higher proportion of active smokers than wives of spousal nonsmokers. This will cause bias in the direction of a positive association. Arguments over the probable size of this bias have occurred with estimated elevations in risk ranging from a few percent to around 50%, depending on assumptions regarding the extent of misreporting, the risk inherent in active smoking, and the degree of marital concordance between smokers (Lehnert, 1984; Wald et al., 1986; Lee, 1987a and b).

Uberla and Ahlborn (1987) raised a number of points regarding the Hirayama study, including those previously mentioned. Citing the "severe selection bias by age," the authors report that the increase in risk with spousal smoking disappears when this bias is corrected for. The study population in fact contained a very small proportion of women aged 70 or more (only about 1%)—so small that the rates generated by nonsmoking married women aged 70 or more are too unstable to provide meaningful results. But by taking the negative results observed in this tiny, unstable stratum of the cohort and weighting them to "correct" for the underrepresentation of this age group, the overall association is made to disappear. Such a "correction" is meaningless. In addition, Hirayama (1990) has noted that the authors inappropriately adjusted to the total female population rather than to the population of currently married females, and characterized the adjustment as "neither of scientific significance nor of creative value."

The authors also essentially take Lee's approach to the differential misclassification problem and claim that a modest differential misclassification "leads to risk ratios of around unity." As seen previously, this argument is plausible but purely speculative—and, of course, potential biases toward the null are ignored in this and other "corrections." The authors conclude that "the null hypothesis . . . is consistent with the Hirayama data in the same way as the alternative." But unless one applies the aforesaid "corrections," the Hirayama data is, in fact, *more* consistent with the hypothesis of association than with the null hypothesis.

Layard and Viren (1989) estimated "projected" mortality rates for a cohort with the age and time distribution found in the Hirayama cohort by applying "standard demographic life table procedures" to year and age-specific life table data from United Nations and Japanese sources.

They concluded that female all-cause and lung cancer reported rates were only 76% and 85%, respectively, of projected values. In a separate analysis, the authors also "calculated the numbers of person-years that would have been observed in the cohort if there had been 100% follow-up" from the reported numbers of deaths. The assumptions used in this calculation are unstated. The authors then estimated, based on the difference between their person-years for 100% follow-up and the reported person-years, and an assumption that 8 years of observation were lost on average for each person lost to follow-up over the 16-year course of the study, that approximately 10% of the cohort was lost to follow-up. Dismissing other possible causes of their estimated mortality deficits, Layard and Viren conclude that "it is possible that biases exist in the data which might invalidate an observed relationship between exposure to ETS and mortality."

Of course, acceptance of Layard and Viren's conclusions must start with acceptance of the validity of their assumptions and calculations, not all of which are stated explicitly. Beyond that, their rejection of alternative explanations for the difference between projected and reported deaths is not convincing. For example, random sampling variation and regional variations in death rates are both dismissed because neither could produce an effect as large as that observed, although the authors' figures indicate that in combination they could well account for a sizeable portion of the difference. Likewise the effect of admitting only (initially) "healthy" people to the cohort is dismissed based on the observation of "still very substantial cohort deficits in the last years of the study" without specification of how substantial such deficits were and ignoring the fact that a pattern in which all-cause mortality is most affected and cancer mortality least, as their calculations showed, is the expected pattern for an effect of selection of healthy individuals. Finally, to produce a spurious association, a bias must operate differently on the exposed (smoking spouse) and unexposed (nonsmoking spouse) groups, and no evidence is provided that supports such a pattern. Lacking such a pattern, the most likely effect of loss to follow-up is a reduction in the observed associations due to missing mortality events. The effect of selecting an abnormally healthy cohort would in a strict sense limit generalizability of conclusions but would not in itself produce an exposure-effect association when none actually existed.

A.13.3. Critique and Assessment

Hirayama's cohort is drawn from a study population assembled to explore the associations between a number of potential health-influencing factors determined via interview and subsequent mortality. Thus, the study was not designed to investigate passive smoking and lung cancer specifically. Most of the weaknesses attributable to Hirayama's study derive from this fact.

The only indicator of ETS available to Hirayama was self-reported smoking status at time of baseline interview. Thus, misclassification of spousal smoking status is possible and change in status over time, modifiers of exposure to spousal smoking, and other sources of ETS exposure cannot be determined.

As previously seen, an overrepresentation of current and former active smokers claiming to be nonsmokers among wives of tobacco smokers probably biases the association between spousal smoking and lung cancer in reported nonsmokers upward. Even the leading proponent of this argument, however, states that unless this bias is much stronger than it appears to be in U.S. and Western populations, it could not account for the major part of the observed results (Lee, 1990). Lack of information regarding amount of smoking actually done in the home and in the presence of the spouse, room size and ventilation, and other exposure modifying factors must lead to imprecision in the estimates of exposure via spousal smoking. This imprecision would make an actual ETS-lung cancer association more difficult to detect. The fact that spousal smoking exposure, even if precisely measured, is an imperfect surrogate for total ETS exposure because workplace and ambient environmental sources are not assessed introduces a similar effect. Both of these problems would thus introduce a bias toward the null, suggesting that the study's results are an underestimate of the real association.

Mortality information was derived from death certificate linkage. It has been contended that lung cancer is routinely overdiagnosed as a cause of death on death certificates, thus undermining the study's credibility. But the resultant misclassification of cause of death would presumably be nondifferential and thus bias results toward the null. To cause overestimation of the association, a greater proportion of women in the spousal smoking groups than in the nonsmoking group would have to be falsely diagnosed as having lung cancer. Because the study cohort was made up of *nonsmoking* women, there would be little reason for such a pattern. (Unless, of course, all such cases came from women who falsely reported their initial smoking status or took up smoking in the course of the study *and* the misclassification/smoking habit concordance hypothesized by Lee were actually strongly at work.)

No information is given regarding whether the same interviewers interviewed both husbands and their wives. Thus, interviewers may not have been blind to spousal smoking characteristics of interviewees. This is likely to have been of little importance, however, because the outcome—lung cancer mortality—was measured prospectively, and thus did not occur for some time *after* exposure had been assessed. If information bias was to some extent operant in the interview, the most likely scenario would find women whose husbands smoked being probed more strongly for admission of their own smoking than were women whose husbands did not smoke.

This would tend to *reduce* underreporting of active smoking in the "exposed" group relative to the "unexposed" group. The result would be to *lower* the observed association between husbands' smoking and lung cancer mortality.

Hirayama's cohort includes only married, reportedly nonsmoking women who were at least 40 years of age and "healthy" at the start of the study. In addition, almost all of these women were under 70 years of age, and agricultural families composed a relatively large part of the cohort. Thus, the cohort does not present a representative cross-section of the Japanese population as a whole. Nevertheless, there is little obvious reason why a relationship between spousal smoking and lung cancer mortality found in this cohort should be dismissed on the grounds that it is not generalizable to the greater Japanese (or other) population. In fact, one could argue that by studying a more homogeneous population in the cohort, the possibilities for bias due to differences between exposed and unexposed groups are reduced.

The possibility that confounding by other risk factors brought about an observed association must be considered in any study. For lung cancer, of course, smoking, gender, and age are major risk determinants. Restriction of comparison groups to same-gender nonsmokers avoids potential confounding by gender or smoking (but see misclassification discussion regarding smoking status). Age is only partially restricted in the study design, so its consideration in the analysis is essential. Hirayama chose to control for husband's age in analyzing the cohort study's results. All observed associations persisted after such adjustment. Spousal ages *should* be closely correlated, but direct adjustment using the subject's own age rather than the age of their spouse would clearly be preferable. One such analysis *was* supplied (Hirayama, 1983b), and in it a significant association between spousal smoking and lung cancer mortality persisted. Furthermore, in analyzing the nested case-control studies, adjustment for wife's age was used throughout, which produced findings that confirmed the results of the cohort study.

The potential role of confounding by other factors in the observed results has received considerable emphasis. A correlation between smoking and lower socioeconomic status with concomitant lifestyle and environmental differences could be expected. Among these differences, particular attention has been paid to the possible effect of dietary factors, particularly low beta carotene intake, and occupational exposures, both of which, some hold, should correlate with spousal smoking and thus could bring about the observed association even if spousal smoking and ETS exposure has no effect. Yet, neither stratification on daily green-yellow vegetable consumption—the best available surrogate for beta carotene intake in the data—nor on agricultural versus nonagricultural occupation of husband eliminated the association between spousal smoking and lung cancer mortality in the cohort study. Similarly, adjustment for husband's occupation and

any of five dietary habit characteristics, along with wife's age, yielded similar results in the case-control approach. Thus, neither of the major proposed confounders satisfactorily accounts for the observed results.

Because the data set does not contain the necessary information to examine confounding due to differences in cooking practices (such as stir-frying), this cannot be ruled out, although such practices might be expected to covary with some of the dietary factors considered in the analyses. Similarly, use of coal for cooking or heating cannot be directly assessed, though a degree of covariance with dietary habits or occupation is likely.

Husband's drinking habits were only marginally associated with lung cancer risk; mortality rates stratified by both drinking and smoking would have been more useful (and stratification by wives own drinking habits would have been more useful still).

When lung cancer mortality among wives is stratified by wife's age (in 10-year increments) and husband's smoking category, a clear dose-response pattern is seen only in the 40 to 49 and 50 to 59 age strata, whereas a decrease in mortality with spousal smoking is seen in the 70 and older stratum. Given that the latter stratum includes less than 1% of the cohort and very few deaths, its rates are too unstable to have much confidence in. The dose-response pattern does become weaker with ascending age strata, however, which has led to conclusions of inconsistency with an ETS-lung cancer connection and presence of confounding. Hirayama has proposed that age-related increases in spousal mortality, smoking cessation, and decreased time spent in husband's proximity during the follow-up period may account for the observed pattern (Hirayama, 1990). The proximity effect seems questionable, because retirement of older husbands would eliminate time spent away from the house at work, but the other arguments are plausible. Alternatively, older women recently married to smokers may be more likely to die from competing causes of death that increase with age before passive-smoke cancer develops. Remarriage, possibly to a spouse whose smoking habits differ from those of the former spouse, would also increase with age and could lead to misclassification of (former) exposure with a bias toward the null. (It is unfortunate that history of former spouses' smoking habits and recency of marriage were apparently not obtained in the baseline interview or the aforementioned problems could be readily addressed.) Temporal trends in some risk modifiers, such as dietary factors, could also play a role.

Confounding cannot entirely be ruled out in certain instances. But the underlying question that must be raised in this regard is the following: *If* the spousal smoking group contains a disproportionate number of individuals with risk-elevating factors such as poor diet, lack of exercise, low socioeconomic status, and occupational hazard exposure, and these factors are

sufficient to produce an increase in lung cancer mortality relative to the spousal nonsmoking group, despite an absence of any real smoking effect, *why* does this multitude of risk factors result in elevations of established smoking-related diseases only and no substantial elevation of risk of other causes of mortality (except brain cancer, which encompasses relatively few deaths)?

In considering the study's results in broader terms, Hirayama's findings are consistent with the hypothesis that exposure of nonsmoking women to passive smoke via spousal smoking increases risk of lung cancer. The observed association is statistically significant. And the persistence of the association after stratification on numerous variables, the observation of a parallel association in nonsmoking husbands of smoking wives, the appearance of associations with other smoking-related diseases, the existence of a dose-response pattern in most analyses of strata containing adequate numbers, and the production of similar conclusions by either cohort or case-control approaches argues against attribution of results purely to chance or confounding.

Possible inclusion of active smokers among "nonsmoking" spouses of smokers through misclassification bias or differential change in smoking status during follow-up remains the study's greatest weakness. This problem could have been addressed by follow-up interviews or questionnaires coupled with verification of smoking status by alternative means in a subsample of the cohort, and still could be. In addition, losses to follow-up and failure to use more sophisticated survival analysis techniques are weaknesses that probably reduced the study's power.

Overall, the Hirayama study provides supportive, although not definitive, evidence that ETS exposure increases lung cancer risk.

A.14. HOLE (Coh)

This prospective cohort study was undertaken in the towns of Paisley and Renfrew, Scotland. The primary objective was to explore the relationship between passive smoking and cardiorespiratory symptoms and mortality, including lung cancer. The towns were selected because they are situated in an area with a high incidence of lung cancer. All persons residing in these towns between 45 and 64 years of age, inclusive, were visited between 1972 and 1976. Each was asked to complete a self-administered questionnaire and to visit a cardiorespiratory screening center where further interviews were conducted; 80% (15,399 persons) responded.

Participating households in which at least two "apparently healthy" subjects lived were included in the study, yielding a study population of 3,960 males and 4,037 females. Data on smoking habits were obtained from the questionnaire and verified by interview at the screening visit. Mortality among subjects was traced using the Scottish National Health Service Central Register and General Register offices (for death certificate linkage), as well as the national cancer

registry system. Results for follow-up through 1982 were published in 1984 (Gillis et al., 1984). The primary results reported here are for follow-up through 1985, published in 1989 (Hole et al.). In addition, the results of unpublished data extending follow-up through December of 1988 are reported (personal communication from Hole to A.J. Wells).

Smoking habits were divided into three categories: persons who have never smoked, former smokers, and current smokers. In addition, the number of cigarettes smoked per day was obtained for current smokers. Both pipe and cigar smokers were excluded from the group who had never smoked. Never-smokers with former or current smokers as cohabitants in their household were classified as passive smokers; otherwise never-smokers were classified as "controls." This classification yielded 1,538 passive smokers and 917 controls for both sexes combined. The corresponding numbers for females alone are 1,295 and 489.

The number of lung cancer deaths among females occurring in the cohort during the follow-up period is only six, too small to be of statistical consequence. The unpublished data extending follow-up through 1988 includes one additional female lung cancer death that occurred subsequent to 1985. The crude relative risk is 2.27 (95% C.I. = 0.40-12.7), which is in the direction of a positive association between ETS exposure and lung cancer. The extremely wide confidence interval is the result of the small number of cancer deaths being compared and indicates that the data could easily arise when the true value of the relative risk is almost any value. After adjustment for age and social class, the relative risk is 1.99 (95% C.I. = 0.24-16.72). Lung cancer incidence was somewhat higher than mortality (10 cases vs. 7 deaths), yielding an adjusted relative risk of 1.39 (95% C.I. = 0.29-6.61). The relative risks for adjusted mortality (5.30) and incidence (3.54) were higher in males than in females but were based on even fewer cases (four deaths, six incident cases).

Although the observed association could easily occur by chance, it is a useful contribution to the pool of evidence on lung cancer and passive smoking. Consequently, it is worth noting that the observed associations are not likely to be attributable to confounding by other factors, because they persisted after control not only for age and gender, but for social class, diastolic blood pressure, serum cholesterol, and body mass index. Thus, differences in lifestyle or environmental factors such as diet, housing, and employment between passive-smoking households and nonsmoking households is an unlikely source of the results. Specific adjustment for potential occupational exposures or radon were not carried out, but these variables would presumably covary with social class to a great extent.

As for other sources of bias, interviewer bias can be discounted because subjects were "apparently healthy" at interview and supplied smoking information before cardiovascular

screening, and the investigators did not begin determining the passive smoking status of subjects until 1983 (for the first published study on this cohort). The extent of loss to follow-up is not specified, so one cannot tell whether this was a potential source of problems. However, linkage was carried out through two registries for general mortality and an additional registry specifically designed for cancers. Diagnoses of cancer mortality from death certificates were checked against cancer registry records for verification, thus reducing potential inaccuracies attendant on use of death certificates.

Some data regarding misclassification were collected in an additional questionnaire administered to a portion of the cohort at some unspecified point in the study. Among controls, 5% said that their household contained a smoker—presumably someone who had not met the inclusion criteria (e.g., age 45-64) for the study. Thus, a small portion of the control group was actually currently exposed, which would produce a slight bias toward the null. Differential misclassification of smokers as never-smokers resulting from concordance of smoking habits among cohabitants cannot be assessed or ruled out, despite the authors' suggestion that persons cohabitating with smokers may be more likely to falsely claim to be smokers themselves, providing a bias toward the null.

In summary, this study appears well-designed and executed, but the number of ETS exposed subjects is small. Although its influence may be relatively small, there are no apparent methodological problems that would limit its usefulness otherwise.

A.15. HUMB

A.15.1. Author's Abstract

"As part of a population-based case-control study of lung cancer in New Mexico, we have collected data on spouses' tobacco smoking habits and on-the-job exposure to asbestos. The present analyses include 609 cases and 781 controls with known passive and personal smoking status, of whom 28 were lifelong nonsmokers with lung cancer. While no effect of spouse cigarette smoking was found among current or former smokers, never smokers married to smokers had about a two-fold increased risk of lung cancer. Lung cancer risk in never smokers also increased with duration of exposure to a smoking spouse, but not with increasing number of cigarettes smoked per day by the spouse. Our findings are consistent with previous reports of elevated risk for lung cancer among never smokers living with a spouse who smokes cigarettes."

A.15.2. Study Description

This population-based case-control study was conducted through the New Mexico Tumor Registry during 1980-84. The original purpose was to explain differing lung cancer occurrence in Hispanic and non-Hispanic whites in New Mexico. The study questionnaire included questions on spousal smoking and on indirect exposure to asbestos through a spouse's job. The current report describes the risks associated with those exposures in smokers and nonsmokers. The data on ETS exposure in nonsmokers is extracted from the larger study containing smokers.

For the whole study, a total of 724 eligible primary lung cancer patients were identified, of which 641 were interviewed (89%). About half (48%) of the case interviews were conducted with the subject. Information on the remaining subjects was obtained from surrogates, generally the surviving spouse or a child. Cases were collected in two series, the first consisting of patients with cancer incident in 1980-82. That group includes all cases less than 50 years of age and all Hispanics, but not those exclusively. The number of cases was supplemented by a second series of patients with cancer incident to a 1-year period beginning November 1983. Most of the controls were selected by random telephone sampling, but some older subjects were randomly selected from Medicare participants. The control group was frequency-matched to the cases for sex, ethnicity, and 10-year age category, at a ratio of approximately 1.2 controls per case. Interviews were held for 784 of the 944 eligible controls, with 98% of the responses from subjects.

The term "never-smoker" means not a cigarette smoker, where the latter is defined to be someone who has smoked at least 6 months. The smoker classification is divided further into current smokers and ex-smokers. The current smoker status includes smokers who have stopped within 18 months prior to the interview; the ex-smoker status applies if smoking ceased more than 18 months prior to interview. Assuming that the minimum 6-month duration of smoking is intended to apply to current and ex-smokers, never-smokers could have smoked previously for up to 6 months.

An ETS-exposed subject is one ever-married to a spouse who smoked cigarettes, regardless of the spouse's use of pipes or cigars. No information was obtained on exposure to ETS from other sources, such as from other household smokers, in the workplace, or from parental smoking during childhood. Measures of ETS exposure from spousal smoking include duration of exposure (in years) and the average number of cigarettes smoked per day by the spouse. The ETS subjects (never-smokers) include 20 (4) female (male) cases and 162 (130) controls (the article reports eight male cases, the number used in much of the analyses, but four of those eight were found to be smokers—personal communication from Humble). The age distribution for the female cases (controls) is as follows: age less than 65, 5 (74); age 65 or more, 15 (88).

The odds ratio for the crude data on female never-smokers is 1.8 (90% C.I. = 0.6-5.4) for spousal smoking of cigarettes only and 2.3 (90% C.I. = 0.9-6.6) when spousal smoking also includes use of pipes and cigars. Based on mean cigarettes per day smoked by the spouse, the odds ratio of 1.2 at more than 20 cigarettes per day is somewhat lower than the odds ratio of 1.8 at the lower rate, less than 20 cigarettes per day. For duration of exposure, the odds ratio increases from 1.6 at less than 27 years to 2.1 at 27 or more years. It is reported that adjustment for age and ethnicity did not alter these results from the crude analysis. A trend test is included for duration of spousal smoking, but the sample sizes are too small to be meaningful. Application of logistic regression to adjust for variables gives values very close to the odds ratios for the crude analyses shown above for spousal smoking, for use of cigarettes only and also for combined use of cigarettes, cigars, and pipes.

The distribution of cases by cell type is given, but only with males and females combined. The ratios of ETS-exposed cases to the total, by cell type, are as follows: squamous cell (2/4), small cell (1/1), adenocarcinoma (either 6/12, 7/12, or 8/12), and others (either 3/3, 2/3, or 1/3, depending on correct ratio for adenocarcinoma).

The authors conclude that the results indicate increased risk from ETS exposure in never-smokers but not in active smokers.

A.15.3. Comments

This study evaluates smokers as well as nonsmokers for increased risk of lung cancer from spousal smoking. Not surprisingly, the number of smokers among the cases far outweighs the number of nonsmokers. No evidence of added risk to smokers from passive smoking is found. Such an evaluation, however, puts a great deal of faith in the exposure data and the power of statistical methods to detect what may be only a marginal increase in risk from ETS on top of active smoking.

Of more central concern to this review is the assessment of lung cancer from ETS exposure in never-smokers. The ETS data are taken from a larger study, so the matching no longer applies, although the adjustment for those variables (ethnicity and age category) in the analysis is worthwhile. The article suggests that the high rate of proxy response for cases in the original study (52%) may be due, at least in part, to inclusion of decedent cases. That topic is not explicitly addressed, however, and controls were not matched to cases on vital status. Never-smokers apparently may have a history of smoking, provided it is under 6 months' duration. Whether any never-smokers actually have a short smoking history is not discussed, but the never-smoker classification is less strict than in most studies.

The data are evaluated a number of different ways, consistently yielding an increased odds ratio. The number of cases, however, is much too small (15 exposed, 5 unexposed) for the observed odds ratio to be close to statistical significance. Although similar values of the odds ratios might be observed in a larger study, that cannot be assumed. At most, the study outcome is suggestive of a possible association between ETS exposure and lung cancer occurrence, in need of additional support to be conclusive. Overall, this study is conducted well in many respects, but its contribution to the pool of evidence for assessment of lung cancer and ETS exposure is tempered by several weaknesses, as described above.

A.16. INOU

A.16.1. Author's Abstract

A case-control study on smoking and lung cancer in women was conducted in Kamakura and Miura, both in Kanagawa prefecture, Japan. The two cities are distinctly different in social environment; the former is a residential community, and the latter is a fishing village. After stratification on city and age groups, the odds ratio of lung cancer in nonsmoking wives was shown to be 1.58 when husbands smoked fewer than 19 cigarettes a day and 3.09 when husbands smoked 20 or more cigarettes a day. For comparison, the odds ratio for active smoking is 5.50. Although the study size is quite small, it provides additional evidence favoring the passive smoking and lung cancer hypothesis. (Paraphrased from author's discussion; no abstract was provided.)

A.16.2. Study Description

This study was conducted to assess the roles of active and passive smoking in the etiology of lung cancer in women. It is unclear how subjects or diagnoses were obtained, but cases are women who died of lung cancer in Kamakura or Miura in the time periods 1980-83 and 1973-81, respectively. Controls, consisting of women who died of cerebrovascular disease during the same time frames, are individually matched to cases on year of birth, year of death ($\pm$ 2.5 years), and district of residence. It is not clear whether incident cases were used.

Face-to-face interviews were conducted by public health nurses and midwives. ETS subjects consist of the 28 nonsmoking cases and 62 nonsmoking controls remaining after elimination of 9 cases and 12 controls who were smokers. Husband's smoking status was not available for unspecified reasons in a total of 8 cases and 20 controls, but these figures include smokers as well as nonsmokers. The exact number of nonsmokers for which spousal smoking status was available is not specified but can be back-calculated from what is given (see below).

No information is given on the number of proxy respondents, the age distribution of the subjects, or attempts to confirm diagnoses of primary lung cancer.

The term "nonsmoker" is not defined, so it is not clear whether it refers to persons who never smoked or who do not smoke at present. Nonsmoking women whose husbands smoke at least five cigarettes per day are classified as exposed to passive smoking. Considerations of former smoking or marital status, ETS exposure at the workplace or in childhood, and duration of exposure are not addressed. No attempts to verify the reliability or validity of the data are mentioned.

The number of subjects is not delineated by case versus control and exposed versus unexposed figures. They can be determined from the odds ratio and confidence interval, however, as 18 out of 22 (exposed over total) cases and 30 out of 47 controls. For nonsmoking women with smoking husbands, the crude odds ratio calculated by the reviewers is 2.55 (95% C.I. = 0.74-8.78). (*Note:* OR = 2.25 is erroneously reported in the article. The OR value of 2.55 has been confirmed by Hirayama.) When husbands' smoking is divided into two strata (< 19 cig./day and 20+ cig./day), the odds ratios increase with exposure from 1.16 to 3.35, giving a statistically significant trend ($p < 0.05$). Age-adjusted odds ratios of 1.39 and 3.16 are reported for the two strata; adjustment for both age and district yields corresponding odds ratios of 1.58 and 3.09. (*Note:* The first OR value, 1.58, is incorrectly reported as 2.58. The value 1.58 has been confirmed by Hirayama.) The authors conclude that, although the study size is quite small, the results provide more evidence favoring the hypothesis that passive smoking causes lung cancer.

A.16.3. Comments

The number of subjects remaining after active smoking and missing data exclusions is small, guaranteeing poor power and lack of statistical significance in the absence of large odds ratios. The details on study design are limited. The source of cases and controls is not mentioned, for example, and it is unclear whether incident or prevalent cases were used.

Information regarding quality control and related concerns is equally sparse. Interviewers used standardized questionnaires, which would help to promote consistency, but no mention is made of blinding them to subject background or study question, the absence of which could introduce interviewer bias (probably in a positive direction). Because cases and controls are stated to have died during the study period, it is probable that proxy respondents were required, but the extent is unknown. In addition, neither duration of ETS exposure from spousal smoking nor exposure from other sources, such as other cohabitants, was considered. The resultant inaccuracy of exposure assessment probably biases the results toward the null. Lack of information on

former smoking status or verification of diagnosis may introduce biases of indeterminate direction. Except insofar as the district acts as a surrogate for factors related to socioeconomic status, no potential confounders other than age or district of residence were considered. The meaning of "nonsmoker" is not given. Was that status left to self-classification? Is some degree of past smoking acceptable? Is smoking history a factor at all (i.e., does nonsmoking refer simply to the current status)? Accurate and meaningful segregation of never-smoking subjects is needed for analysis, but there is no indication that that was accomplished.

Although a substantial odds ratio was observed for husband's smoking, these results are based on a small sample with too few details provided to assess adequately either the evidence or the study's design and execution. The numerous sources of potential bias are enhanced by the omissions or sketchy descriptions of the study. The statistical uncertainty of the odds ratios given is reflected in the extremely wide confidence intervals shown. The test for trend does not add any additional information. It is basically a restatement of the significant comparison between the heavily exposed group (husband smokes > 20 cig./day) and the unexposed group. Unfortunately, the brevity of the description of this study in the source available severely limits its utility.

A.17. JANE

A.17.1. Author's Abstract

"The relation between passive smoking and lung cancer is of great public health importance. Some previous studies have suggested that exposure to environmental tobacco smoke in the household can cause lung cancer, but others have found no effect. Smoking by the spouse has been the most commonly used measure of this exposure.

In order to determine whether lung cancer is associated with exposure to tobacco smoke within the household, we conducted a population-based case-control study of 191 patients with histologically confirmed primary lung cancer who had never smoked and an equal number of persons without lung cancer who had never smoked. Lifetime residential histories including information on exposure to environmental tobacco smoke were compiled and analyzed. Exposure was measured in terms of "smoker-years," determined by multiplying the number of years in each residence by the number of smokers in the household."

A.17.2. Study Description

This study was undertaken in New York State to clarify the role of exposure to tobacco smoke in the household as a possible cause of lung cancer among nonsmokers. Interviews were conducted with former as well as never-smokers initially (Varela, 1987), but because matching

was carried out on smoking status, only never-smoking case-control pairs were included in the analyses for this article. The study includes both males and females, which are combined in all of the analyses. There are 146 (45) female (male) pairs.

Cases are never-smokers aged 20 to 80 years newly diagnosed with lung cancer at 125 referral centers in New York from July 1, 1982, to December 31, 1984. Controls are cumulatively sampled never-smokers identified from files of the New York Department of Motor Vehicles. Controls are individually matched to cases on age (± 5 years), gender, and residence. In addition, the same interview type (proxy or direct) was used for controls as for their corresponding cases. Exposure data were collected face-to-face via standardized questionnaire by interviewers blind to the subject's status.

From the 439 case-control pairs interviewed, 242 pairs containing former smokers and 6 pairs with a mismatch on the source of response were excluded. Of the remaining 191 pairs used in the ETS study, interviews were conducted directly with the subjects in 129 (68%) and with proxies in 62 (32%) (if a proxy was interviewed for a case, then a proxy was used for the matching control as well). No demographic comparisons were provided for the ETS cases and controls. For the whole study including smokers, the mean age of cases and controls is nearly identical (67.0 and 68.1, respectively; Varela, 1987). Histological verification of diagnosis was obtained for all but five cases (for whom only clinical information was available) out of the initial population of 439.

Persons smoking no more than 100 cigarettes over the course of their lifetime qualified as never-smokers for this study. Cigar or pipe smoking was apparently not considered. Exposure to ETS was deemed to occur when a smoker lived in the subject's household at any time from infancy to adulthood. Both total household smoke exposure and spousal smoke exposure were determined. Preadult (before 21 years of age) and adult exposure were examined separately. Exposures were computed in units of "smoker-years," the total number of years lived with each smoker summed over smokers. In addition, pack-years were calculated for spousal smoking. Workplace exposure also was estimated by smoker-years, whereas exposure in social settings was estimated subjectively on a scale from 1 to 12 for each decade of life and summed. Exposure data were not checked, and marital status was not considered in the analyses. No information on tumor type or location was provided for the never-smoking population.

Preadult exposure to 24 or more smoker-years occurred in 52 (29) cases (controls) whereas 82 (94) were exposed to 1 to 24 smoker-years and 57 (68) were unexposed. Odds ratios were calculated using matched-pairs regression analysis. Preadult passive smoking yielded increasing odds ratio of 1.09 (95% C.I. = 0.68-1.73) for 1 to 24 smoker-years and 2.07 (1.16-3.68) for 25 or more smoker-years. The odds ratios for adult exposure are low but also increase—from 0.64 (0.34-

1.21) at 1 to 24 smoker-years to 1.11 (0.56-2.20) at 75 or more smoker years. The odds ratios for lifetime exposure increase from 0.78 (0.36-1.67) at 1 to 24 smoker-years to 1.80 (0.83-3.90) at 25 to 99 smoker-years and then dip to 1.13 (0.56-2.28) at 100 or more smoker-years. Spousal smoking was not significantly associated with lung cancer. In fact, when results were stratified by type of interview, proxy interviews yielded strong and, in some instances, statistically significant *negative* associations for spousal smoking, with odds ratios between 0.20 and 0.68 for ETS expressed in terms of present or absent, smoker-years, and pack-years of exposure. The odds ratios for direct interviews, in contrast, range from 0.71 to 1.10 and are uniformly higher than the odds ratios for corresponding proxy responses. Workplace exposure to 150 or more person-years yielded an odds ratio of 0.91 (0.80-1.04), whereas a social setting exposure score of 20 led to a statistically significant *decreased* odds ratio of 0.59 (0.43-0.81).

The authors conclude that they found a significant adverse effect of relatively high levels of exposure to ETS during early life (before age 21). For those who were exposed to 25 or more smoker-years in their first two decades of life, the risk of lung cancer doubled. By contrast, they found no adverse effect of exposure to ETS during adulthood, including exposure to a spouse who smoked. This lends further support to the observation that passive smoking may increase the risk of subsequent lung cancer, and it suggests that it may be particularly important to protect children and adolescents from this environmental hazard.

A.17.3. Comments

The number of never-smoking cases is relatively large, resulting in above-average statistical power for evaluation of ETS effects. Controls were matched to cases on smoking status, as well as the key demographic factors of age, gender, and neighborhood. Comparability of cases and controls was likely good, as evidenced by the similar mean ages for the total population, although no other comparative information is available. Interviews were ostensibly conducted blindly, thus precluding interviewer bias, but in view of the use of population-based, basically healthy controls, it is questionable that diagnostic blinding was effective. The study's matching on smoking status with subsequent retention of matching and use of matched-pairs analysis for ETS exposure effectively eliminates potential confounding by age, gender, or residence, and makes confounding by related factors (such as socioeconomic status) less likely. A rare feature is the use of matching on interview type (i.e., proxy or subject direct), thus eliminating potential confounding by this source. Comparison of spousal smoking results for direct and proxy interviews, however, indicates consistently lower estimated risks from proxies. This suggests that use of proxy respondents did not merely lead to increased random misclassification but might

have biased the outcome toward a negative association. The authors posit that proxies of lung cancer patients may be more likely to underreport exposure than those of control subjects. Curiously, however, although the authors report that odds ratios "frequently differed according to type of interview," they do not specify how the odds ratios differed for exposure other than spousal smoking. Also, the composition of the proxy groups—relative proportions of spouses, other relatives, and friends or associates—is never discussed, leaving unexplored the possibility that misreporting by spouses of cases may lie at the heart of the observed discrepancy. It is also interesting that the outcome of self- versus proxy responses in this study is in the opposite direction of the findings in GARF. Diagnostic misclassification is unlikely, given the histological verification of nearly all cases.

The restriction of subjects to persons smoking no more than 100 cigarettes in their lifetime theoretically eliminates active smoking as a source of bias, although no verification of smoking status was undertaken. Consideration of potential sources of ETS exposure is commendably thorough, and the calculation of total years of living with smokers, regardless of relation to the smoker, as an index of household smoke exposure minimizes the possibility that any source (e.g., roommates) is overlooked. In contrast, the index of exposure in social settings is highly subjective, and persons more habituated to passive smoke may report a given exposure as less severe than persons less accustomed to smoke, thus creating a negative bias. The proportion of controls classified as exposed to ETS is 80%, which is high in comparison to other studies. This suggests that some exposed controls may have only minor exposure to ETS, making detection of an association (if present) less likely. Unlike almost every other ETS study, males and females are combined in the analysis and only the joint results are reported. Because there are 45 (146) pairs of males (females), the sample sizes are sufficient to warrant reporting odds ratios separately by sex and to test the hypothesis of no difference due to gender.

Lung cancer odds ratios for adulthood, lifetime, and spousal smoking are consistently well below one for low ETS exposure relative to nonexposure, as if exposure had a protective effect. Thereafter, however, the odds ratios associated with increasing levels of exposure are suggestive of an upward trend in response. Although we would not dismiss the occurrence of this outcome as attributable to chance alone, it is consistent with the baseline lung cancer mortality rate in the control population simply being higher than that of the case population for reasons other than exposure to spousal smoking. A pervasive (systematic) negative bias linked with exposure could also produce such an effect. Both of these contingencies are speculative, however, because there is no evidence in the article to support either, aside from the outcome of the data. Further fueling the speculation, however, are the markedly lower odds ratios obtained from surrogate responses,

indicative of some source of bias acting unequally on proxy and nonproxy sources. Also speculative is the idea that using predicted responses from a model that fits the data poorly might produce such an effect, but that level of detail is beyond the scope of most published articles, including this one. Some explanatory discussion by the authors on these issues, as well as *separation of the analyses by sex*, would enhance interpretation of results and facilitate comparison with results of other studies on females.

The authors' finding that exposure during childhood and adolescence appears to influence subsequent lung cancer risk more than exposure during adulthood raises some interesting possibilities. More time may be spent in proximity to a household smoker (particularly the mother), on average, in childhood than in adulthood. According to data presented by K.M. Cummings (Roswell Park Memorial Institute, Buffalo, NY) at the Science Advisory Board meeting on EPA's draft ETS report (U.S. EPA, 1990), on December 4-5, 1990, heavy childhood exposure is a better surrogate for total lifetime exposure than is spousal exposure. Also, early exposure may appear to become a risk, either due to a long latency period for lung cancer or, perhaps, due to increased susceptibility at an earlier age. The results suggesting an effect from early exposure but not from spousal smoking are more nearly atypical than reinforced by other studies, though, and the number of exposure sources considered raises the possibility that the strength of association seen for preadult exposure may be due to chance. However, after elimination of 78 pairs with incomplete marriage or household exposure data, the association persisted and was strengthened (OR = 2.59), arguing against chance as the major influence. It is unclear what role, if any, negative bias due to proxy respondents may have had in the nonspousal analyses.

In summary, the findings for preadult exposure are not readily attributable to chance or confounding, although some role of interviewer bias or unmeasured confounding factors such as diet cannot be ruled out. No association with lung cancer incidence is observed for spousal smoking. The authors conclude, however, that, spousal smoking aside, other sources of household ETS exposure support the conclusion that exposure to ETS can cause cancer. That conclusion is not unequivocal in our view. In general, the odds ratios (aside from preadulthood exposure) tend to be low but trend upward with exposure, exhibiting more of a patterned response than one might expect to see due to randomness. This is puzzling as there is no apparent source of bias and the study appears to have been conducted with considerable forethought and thoroughness. The only exception noted is the lack of separate analyses and comparisons of males and females. These concerns notwithstanding, the study is a useful addition to the literature on ETS exposure and lung cancer.

A.18. KABA

A.18.1. Author's Abstract

"Among 2,668 patients with newly diagnosed lung cancer interviewed between 1971 and 1980, 134 cases occurred in 'validated' nonsmokers. The proportion of nonsmokers among all cases was 1.9% (37 of 1,919) for men and 13.0% (97 of 749) for women, giving a sex ratio of 1:2.6. Kreyberg Type II (mainly adenocarcinoma) was more common among nonsmoking cases, especially women, than among all lung cancer cases. Comparison of cases with equal numbers of age-, sex-, race-, and hospital-matched nonsmoking controls showed no differences by religion, proportion of foreign-born, marital status, residence (urban/rural), alcohol consumption or Quetelet's index. Male cases tended to have higher proportions of professionals and to be more educated than controls. No differences in occupation or occupational exposure were seen in men. Among women, cases were more likely than controls to have worked in a textile-related job (relative risk = 3.10, 95% confidence interval 1.11-8.64), but significance of this finding is not clear. Preliminary data on exposure to passive inhalation of tobacco smoke, available for a subset of cases and controls, showed no differences except for more frequent exposure among male cases than controls to sidestream tobacco smoke at work. The need for more complete information on exposure to secondhand tobacco smoke is discussed."

A.18.2. Study Description

In 1969, the American Health Foundation began interviewing newly diagnosed lung cancer patients with cancer at sites potentially related to tobacco use for a case-control study that is still ongoing (Wynder and Stellman, 1977). The current article considers the data on lung cancer in nonsmokers alone collected from newly diagnosed lung cancer patients between 1971 and 1980. Several factors are of interest: histology, demographic factors, residence, Quetelet's index, alcohol consumption, previous diseases, occupation and occupational exposures, and ETS exposure. The number of nonsmokers among the cases is small, so the authors consider the results to be preliminary.

The study from which the data on lung cancers in nonsmokers are extracted is a very large effort that includes tobacco-related cancers at multiple organ sites and includes smokers as well as nonsmokers. The cases are from approximately 20 hospitals in 8 U.S. cities (about one-third from New York City). With reference to the lung cancer cases in that study, histologic type of lung cancer was determined from pathology reports and discharge summaries. Secondary lung cancer cases were excluded. Controls consist of hospital patients with diseases unrelated to tobacco use who were pair-matched with cases on hospital, age (within 5 years), sex, race (with five

exceptions), date of interview (within 2 years), and nonsmoking status. Cases appear to be incident, and control sampling is density. All subjects were interviewed while patients were in the hospital. The questionnaire for the interviews was expanded in 1976. Questions on exposure to ETS were not included, however, until an addendum to the questionnaire in 1978, which was then modified in 1979.

The term "nonsmoker" applies to subjects who have smoked less than one cigarette, pipe, or cigar per day for a year. The term "never-smoker" is used interchangeably. Independent of the intended definition, however, subjects whose hospital charts indicated any record of smoking, even in the remote past, were excluded from the nonsmoker classification. ETS subjects include 53 (25) females (males), after combined attrition of 22 (9 without primary lung cancer and 13 with a record of smoking). The age distribution of the female cases (controls) is as follows: age less than 50, 12 (15); age 50 to 59, 26 (24); age 60 to 69, 29 (34); age 70 or more, 30 (24). Histologic data on lung cancer type are given for female cases: squamous cell (16), adenocarcinoma (60), alveolar (12), large cell (4), and unspecified (5). The authors report that exposed cases did not differ from the unexposed cases in the distribution of histologic type.

A person is "ETS exposed" (1) at home, if currently exposed on a regular basis to family members who smoke, (2) at work, if currently exposed on a regular basis to tobacco smoke at work, and (3) to spousal smoke, if the spouse smokes. There are data on 53 cases and their controls for exposure at home and at work, but data on only 24 cases and 25 controls for spousal smoking. This is because of the change in the questionnaire from 1978 to 1979 and because spousal smoking was only applicable for women currently married. Because nonsmoking status was a variable for matching, the 53 pairs of cases and controls for analysis of exposure at home or at work are matched; the data for spousal smoking, however, are technically not matched. There is no indication at all of an association between ETS exposure and lung cancer for women from exposure at home, at work, or from spousal smoking. For ETS exposure at home, there are 16 out of 53 (exposed/total) cases and 17 out of 53 controls; for exposure at work, the figures are 26 out of 53 cases and 31 out of 53 controls; and for spousal smoking, the data are 13 out of 24 cases and 15 out of 25 controls. No statistical calculations are provided for females. From cur calculations, the odds ratio for spousal smoking is 0.79 (95% C.I. = 0.25-2.45). (Among male subjects, exposure to ETS in the workplace was slightly significant, $p = 0.05$, as reported in the article.) For other potential risk factors for lung cancer in women other than passive smoking, it was found that cases were more likely than controls to have worked in a textile-related job (OR = 3.1; 95% C.I. = 1.1-8.6), but the significance of the finding was not clear. It was also found that more female

cases had a history of pneumonia compared to controls, but no interpretation could be attached to the observation.

A.18.3. Addendum

Unpublished preliminary results of a study of ETS and lung cancer in never-smokers conducted at the American Health Foundation have been reported at two meetings—The American Public Health Association (APHA) 119th Annual Meeting, Atlanta, Georgia, November 10-14, 1991, and The Toxicology Forum, 1990 Annual Winter Meeting, Washington, D.C., February 19-21, 1990. A completed report for our review was not available at the cutoff date for inclusion in this document (personal communication with the first author, Dr. G.C. Kabat). Enclosed below is the abstract for the APHA meeting.

RISK FACTORS FOR LUNG CANCER IN LIFETIME NON-SMOKERS
Geoffrey C. Kabat, Ernst L. Wynder

Risk factors for lung cancer in lifetime non-smokers (NS) were assessed in a hospital-based case-control study carried out between 1983 and 1990. The study population consisted of 41 male and 69 female NS cases and 117 male and 187 female NS controls matched on age, race, hospital, and date of interview. Evidence of an effect of exposure to environmental tobacco smoke (ETS) was inconsistent. In males, there was no difference between cases and controls in reported exposure to ETS (yes/no) in childhood, in nonsignificant association with exposure in childhood (OR = 1.6, 95% C.I. 0.9-2.8), but no association with exposure in adulthood at home or at work. Male cases were somewhat more likely to have a smoking spouse (OR = 1.6, 95% C.I. 0.7-3.9), whereas there was no difference in females. Cases and controls did not differ in reporting a history of previous respiratory diseases. Female cases were more likely to report a history of radiation treatment (OR = 4.3 95% C.I. 1.5-12.3). In females, but not in males, a significant inverse association was observed between body mass index (based on self-reported weight 5 years prior to diagnosis) and lung cancer risk.

A.18.4. Comments

Although the study contains more than 2,600 patients, only a small number of nonsmokers are available because questions about ETS exposure were not included in the interview until 1978 and the questions were changed in 1979. It is not clear just how the questionnaire was changed, although the general tenor of the article suggests care in study planning and execution. The design for the larger study from which the ETS data are taken is pair-matched on numerous factors of potential interest, including "nonsmoking status," which contributes favorably to the analysis of ETS data alone. Cases with secondary tumors were excluded, histological type was considered, and all subjects were personally interviewed. It appears that only the currently married females were included in the question regarding exposure to spousal smoke, which

alleviates the need to make some approximating assumptions regarding exposure of widows, singles, and so forth.

Two potential concerns about the analysis of ETS subjects have to do with the definition of "ETS exposure" and "nonsmoker." It is noted that duration of smoking was comparable in cases and controls, but interview questions regarding exposure to ETS refer only to current exposure (this is not explicit in the article but was confirmed by the first author). Also, this measure of exposure has no units (e.g., number of cigarettes per day or pack-years smoked by spouse), which might leave the question less subjective and perhaps help to dichotomize on ETS exposure more sharply. Because lung cancer may have a latency period of 20 years or so, exposure in the past, both in terms of duration and intensity, may be more meaningful than recent exposure. With regard to the definition of nonsmoker, the requirement is less rigid than is often imposed. Ever-smokers are included provided they did not smoke more than the equivalent of 1 cigarette per day for 1 year (about 18 packs). Smoking may seriously confound ETS exposure, and it is difficult to know what constitutes a "negligible" level of past smoking.

One of the factors of interest to the investigators is occupation, so cases and controls were not matched on that variable. For ETS exposure, occupation could be a potential confounding factor. Among females, the controls contain a higher percentage of professional and skilled workers than do the cases (47 to 25), and a lower percentage of housewives (41 to 50). Some differences are also apparent in religious preference between cases and controls that may bear some influence through lifestyle or dietary practices. Variables such as these may need to be taken into account in an adjusted analysis when more data become available.

As noted previously, this article is presented as a preliminary report, and it should be interpreted in that light. The data set on ETS subjects is small. We expressed some reservations about the operational meaning of "nonsmoker" and "ETS exposed," both of which could be more strict. Nonsmokers may have a light history of smoking; exposed nonsmokers may have very little history of exposure. Both factors may be sources of bias, the second one toward the null hypothesis of no effect, and the first one possibly in either direction. This study contributes some useful evidence for the epidemiologic evaluation of whether ETS poses a detectable lung cancer risk, but the potential for bias and the uncertainty due to small sample size could be influential.

A.19. KALA

A.19.1. Author's Abstract

"A case-control study was undertaken in Athens to explore the role of passive smoking and diet in lung cancer, by histologic type, in non-smoking women. Among 160 women with lung

cancer admitted to one of seven major hospitals in Greater Athens between 1987 and 1989, 154 were interviewed in person; of those interviewed, 91 were life-long non-smokers. Among 160 identified controls with fractures or other orthopedic conditions, 145 were interviewed in person; of those interviewed 120 were life-long non-smokers. Marriage of a non-smoking woman to a smoker was associated with a relative risk for lung cancer of 2.1 (95% confidence interval [CI] 1.1 — 4.1); number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data collected through a semi-quantitative food-frequency questionnaire indicated that high consumption of fruits was inversely related to the risk of lung cancer (the relative risk between extreme quartiles was 0.27 (CI 0.10 — 0.74). Neither vegetables nor any other food group had an additional protective effect; furthermore, the apparent protective effect of vegetables was not due to carotenoid vitamin A content and was only partly explained in terms of vitamin C. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma."

A.19.2. Study Description

This study was undertaken in Athens, Greece, in 1987-89. It sought to explore the role of passive smoking and diet in the causation of lung cancer in nonsmoking women. All data used in the study were collected specifically for that purpose.

Cases are never-smoking women hospitalized in one of seven Greater Athens area hospitals during an 18-month period of 1987-89 with a definite diagnosis of lung cancer from histologic, cytologic, or bronchoscopic exam. Controls were selected from female never-smoking patients in the orthopedic ward of the same seven hospitals and an orthopedic hospital. A control was interviewed within 1 week of a corresponding case, thus essentially density-sampled but otherwise unmatched. Cases were not specifically restricted to incident cancers. All subjects were interviewed face-to-face by one of five trained interviewers; interviews were apparently unblinded. A total of 160 lung cancer cases and an equal number of controls were initially identified; 6 cases and 12 controls were too ill to interview, whereas 3 controls and no cases refused to participate. After exclusion of smokers, 91 cases and 120 controls remained. The age distributions of the cases and controls are very similar: for cases and controls, 16.5% (14.2%) were less than 50 years of age, 19.8 (18.3%) were 50 to 59, 29.7 (25.8%) were 60 to 69, and 34.1 (41.7%)

were 70 or older. Current residence, level of education, occupation (housewife vs. other) and marital status were also similarly distributed between cases and controls. Case diagnosis was established by histology (48%), cytology (38%), or bronchoscopy (14%), with exclusion of cancers diagnosed as secondary.

Persons reportedly smoking fewer than 100 cigarettes in their lifetime are classified as nonsmokers. No mention is made of pipe or cigar smoking. Several different sources of ETS exposure are considered: husbands who smoke quantified in terms of years exposed and average number of cigarettes smoked per day; household members *other* than husbands who smoke, quantified by the sum of years exposed to each smoker; and coworkers who smoke, measured by the number of smokers sharing the "same closed space" as the subject. Presumably childhood exposure is included in the household exposure assessment. For spousal smoking, single women are considered unexposed, whereas exposure of widowed or divorced women is based on their married period. No attempts to verify exposure are mentioned.

For analysis of husband's smoking based on cigarettes per day, 64 out of 90 (exposed/total) cases and 70 out of 116 controls gives a crude odds ratio of 1.6 for 90 cases and 116 controls; 64 cases and 70 controls were exposed. The authors present results stratified by four exposure categories, which indicate no significant association ($p = 0.16$). Crude data for husband's smoking stratified by five levels of smoking duration (never, < 20, 20-29, 30-39, and 40+ years) yield a marginally significant increase in association with increasing duration ($p = 0.07$), with odds ratios of 1.0, 1.3, 1.3, 2.0, and 1.9, respectively. No statistically significant association was noted for ETS exposure from other household members ($p = 0.60$) or for exposure at work ($p = 0.13$), but the crude odds ratios for these exposures were 1.41 and 1.39, respectively. Stratification by level of intake for each of 16 food and nutrient groups yielded a significant negative (favorable) association with cereals ($p = 0.04$) and a possible association with fruits ($p = 0.11$).

Multiple logistic regression was then used to adjust results for age, education, and interviewer. An adjusted relative risk estimate of 1.92 (95% C.I. = 1.02-3.59) was obtained for marriage to a smoker. After adjustment, trends for estimated lung cancer risk showed an increase with duration of exposure (average 16% per 10 years) and packs per day (6% per pack), but these were not statistically significant. No trend was observed for ETS in the household or workplace. Adjustment for other sources of air pollution had no effect on the analyses. Adjustment of dietary analyses for age, education, interviewer, and total energy intake indicated a significant decrease in estimated risk between highest and lowest quartiles of consumption of fruit ($RR = 0.33$; $p = 0.02$) and a nearly significant increase with consumption of retinol ($RR = 1.31$; $p = 0.06$), whereas beta carotene ($RR = 1.01$) and other dietary factors had no significant effect.

Adding fruit consumption to the model for passive smoking increased the adjusted relative risk for husband's smoking slightly, from 1.92 to 2.11. Stratification by lung cancer cell type yielded somewhat lower adjusted estimated relative risks for adenocarcinoma (2.04) than for squamous, small, and large cell cancer combined (2.58). No adjusted results were presented for other household or workplace exposure.

The authors' conclusion is best reflected in their abstract (shown in full above). Marriage of a nonsmoking woman to a smoker was associated with a relative risk for lung cancer of 2.1. Number of cigarettes smoked daily by the husband and years of exposure to husband's smoking were positively, but not significantly, related to lung cancer risk. There was no evidence of any association with exposure to smoking of other household members, and the association with exposure to passive smoking at work was small and not statistically significant. Dietary data indicated that high consumption of fruits was inversely related to the risk of lung cancer. Neither vegetables nor any other food group had an additional protective effect. The associations of lung cancer risk with passive smoking and reduced fruit intake were independent and did not confound each other. Passive smoking was associated with an increase of the risk of all histologic types of cancer, although the elevation was more modest for adenocarcinoma.

It is noted that these findings are compatible with the relatively low incidence of lung cancer in the Greek population—a population with the highest per capita tobacco consumption in the world, but with a very high fruit consumption as well.

A.19.3. Comments

This study was generally well designed and executed. Set up specifically to address passive smoking and diet as etiological factors in lung cancer, it includes sufficient numbers of nonsmoking women to produce substantive results. Interviews were face-to-face and no proxies were used, enhancing accuracy and comparability of responses, whereas the very low rate of refusal minimizes potential bias due to volunteer selection. Cases and controls were very similar demographically, were drawn from most of the same hospitals, and were matched temporally on time of interview, so comparability seems high. Furthermore, the study hospitals' patient population accounts for the majority of lung cancer and trauma patients seen in the Athens area, enhancing generalizability of results. Most lung cancers were histologically or cytologically confirmed, reducing chances for misclassification of disease status.

On the debit side, the apparently unblinded interviews could have been biased (although what can be accomplished toward that end is limited). Adjustment for interviewer in the analyses did not affect the results, however, and it is unlikely that all interviewers would share the same

bias. Determination of what constitutes workplace exposure is vague, and childhood exposure is not clearly differentiated from adult household exposure; these were notably the passive smoking categories, which showed the least association with lung cancer. ETS exposure in the workplace is analyzed with regard to trend (Table 2), with levels of exposure represented by "housewife" (zero exposure), "minimal," and "some," resulting in a p value of 0.13. Perhaps correctly, the authors cautiously note the evidence that ETS exposure is associated with increased risk (referring to Table 2 in general, not just exposure at work) but indicate that the differences are not large enough to be interpretable without controlling for confounding effects. An analysis of exposed versus unexposed for the workplace may have been useful, especially an adjusted analysis. Our calculation of the crude odds ratio for a comparison of "minimal" and "some" exposure at work is 1.7, which is suggestive.

Methodological rigor and thoroughness are particularly evident in the treatment of potential sources of confounding. Despite the demographic similarity of cases and controls, the key demographic variables of age and education were nevertheless controlled for in the analyses, along with interviewer identity. Air pollution, total energy intake, and other dietary factors were also examined as potential confounders, and the impact of cancer type was evaluated. An association of husband's smoking with lung cancer yielding an odds ratio of around 2 persisted throughout. The authors claim to have taken special effort to exclude ex-smokers from misclassification as never-smokers, taking account of this potential source of upward bias. No discussion was found, however, of what measures were taken to control misclassification of former smokers as never-smokers, beyond interviewing subjects about current and former smoking habits.

In summary, this study presents evidence of a level- and duration-dependent association between husband's smoking and lung cancer in a well-defined and highly comparable group of Greek cases and controls. Positive but nonsignificant relationships with general home or workplace passive smoking were observed, and there are indications that additional analysis of workplace exposure may be worthwhile. No effect of air pollution was observed. With regard to dietary factors, the large number of potential factors considered raises the issue of multiple comparisons. Fruit consumption may be a significant factor, but further evidence is needed to firmly establish this, particularly in view of the number of dietary factors explored. Dietary factors, however, do not account for the results for ETS exposure in this study. The results regarding spousal smoking cannot be readily attributed to bias, and they provide good quantitative data on the issue of passive smoking and lung cancer. This well-conducted study makes a valuable contribution to the evidence on lung cancer and ETS exposure.

A.20. KATA

A.20.1. Author's Abstract

"It is becoming noticeable in Japan that with increased incidence of lung cancer, there has been an increase in pulmonary carcinoma in women. Active smoking by women is increasing, while concern over passive smoking has been intensifying, and the effect of passive smoking on carcinogenesis had become a social problem. Regarding this effect, immunological and public health reports have appeared in Japan, but there have been few clinical reports, and detailed analysis of patients has been inadequate. Lung cancer presents a variegated histological picture, and presumably there are different carcinogenic factors for different histological types, although there have also been few reports on this subject. The effect of passive smoking probably varies depending on the regional environment and custom, and these factors should also be analyzed and included in the investigation. The present report describes our findings regarding the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women."

A.20.2. Study Description

This study was undertaken in the Nara Prefecture, Japan, to investigate the effects of smoking and familial aggregation of cancer in cases of pulmonary carcinoma in women. Active smokers are included in the study, from which the nonsmokers are drawn for analysis. Matching is retained, however, in the nonsmokers.

For the whole study, subjects were drawn from a hospital (presumably the Nara Prefecture Medical University Hospital) during an unspecified period of time. Cases are female patients with histologically diagnosed lung cancer; controls are female patients with "non-malignant" disease, matched 2 to 1 with cases on age plus or minus 2 years. It is not clear if only incident cases were used and if controls were density sampled. Case diagnoses were obtained from histological exam results, whereas control diagnoses were presumably from medical charts. Other information was collected from apparently unblinded "questioning," with an unspecified degree of reliance on proxy responses from family members.

A total of 25 cases and 50 controls are included in the study; no information on refusals is provided. Exclusion of active smokers leaves only 17 cases and, with retention of 1:1 matching, 17 controls. Mean ages for the total study population are 67.5 ± 8.8 years (67.6 ± 8.5 years) for cases (controls). The age distribution of ETS subjects is not discussed. Nonsmokers are defined by exclusion of "active smokers," with no delineation between former and current smokers. ETS exposure is defined as exposure to smoking more or less daily through living with a smoker. Three periods of ETS exposure are considered: current, past, and childhood, the last for those

"exposed since early childhood." Clearly these types are not mutually exclusive, although current sources of exposure are omitted from the "past" exposure category, even if present for a long time.

ETS exposure is quantified as cigarettes per day smoked times number of years. No mention is make of cigar or pipe smoking, nor of checks on exposure data. No distinction is made regarding marital status. Tumors occurring among current passive smokers were mostly adenocarcinomas (13/17), the remainder (4/17) being squamous or small cell cancers. Airway proximity was not specified. Excluding active smokers, all 17 cases were current passive smokers, compared to 14 out of 17 controls, for an odds ratio of 1.2, whereas past passive smoking characterized 16 of 17 cases and 17 of 17 controls, for an odds ratio of 0.9 (these odds ratios reflect the substitution of 0.5 for 0 in the exposure categories in which no subjects fall). Childhood passive smoking was reported in 13 of 15 cases and 7 of 15 controls (apparently all those for whom information was available), for an odds ratio of 7.4 ($p < 0.1$). None of the passive smoking odds ratios was statistically significant at the 5% level. No definite conclusion can be drawn from the present study, but there is a suggestion that passive smoking is associated with development of lung cancer in the Nara region. The effect of passive smoking that continued to the present time was especially marked, particularly in squamous cell carcinoma and small cell carcinoma. With adenocarcinoma, an effect of passive smoking in the past is suspected. Along with passive smoking, the association of some intrinsic factor (genetic tendency) to varying degrees in the different histologic types of lung cancer in women, especially in adenocarcinoma, is apparent.

A.20.3. Comments

The histological diagnosis of all cases, in combination with the apparent involvement of the researchers in the diagnoses, virtually eliminates the potential pitfall of misclassification of lung cancer cases. It also allows specific breakdowns by cell type. With regard to passive smoking, however, limitations related to exclusion of active smokers greatly reduced the study's potential.

In their initial analyses, the authors investigate passive smoking without excluding or stratifying on active smoking and report statistically significant associations with lung cancer and combined effects with family history of cancer. This is not a meaningful analysis, because the effects of active and passive smoking cannot be separated and because passive smoke exposure probably correlates strongly with extent of active smoking. Excluding active smokers greatly reduces the available numbers of matched subjects and, in combination with the very high exposure prevalence among qualifying controls, makes the differences between cases and controls

highly unstable for all comparisons except for that of childhood exposure. Even here, with an estimated relative risk of 7.4, the results do not reach the 5% level of statistical significance, notwithstanding the problem of multiple comparisons. This does not deter the authors from attempting cell-type-specific analyses, but these too fail to yield significant results. The extraordinarily high proportion of exposed present and past passive smoking controls is apparently a fluke, because the proportion is not as high in the total control subject population (or childhood passive smoking controls). Nevertheless, exposure was very common among controls. This indicates that the exposure criteria may be too lax or, alternatively, that the control population included a substantial proportion of persons with smoking-related diseases (controls being only stipulated not to have malignant disease).

In light of the minimal utility of the study's passive smoking analyses, detailed consideration of design strengths and weaknesses is unwarranted. Major points not already mentioned relate to information ascertainment and confounding. Interviews were apparently unblinded and, especially if conducted by the authors themselves, may thus have been biased toward uncovering exposure among cases (although the high prevalence of exposure among controls as well as cases argues against this). Furthermore, the extent of proxy interviews, potentially decreasing accuracy of exposure assessment, is unclear.

All subjects are female and, although results are not age adjusted, matching on age was retained for all analyses. No other potential confounders except family history of cancer were considered, probably due to limited subject numbers, because much information on potential confounders was collected. Moreover, family history was considered only in the nonmeaningful analyses, which did not differentiate active and passive smokers. Thus, although the problems with numbers and exposure misclassification probably reduced the study's ability to detect whether an association exists, information bias and confounding could have biased results either up or down.

In summary, this study's data are consistent with an association of passive smoking, particularly childhood exposure, with lung cancer, but the results are too unstable and subject to potential bias to carry much weight, and the quantitative results must be viewed with extreme caution.

A.21. KOO

A.21.1. Author's Abstract

"Lifetime exposures to environmental tobacco smoke from the home or workplace for 88 "never-smoked" female lung cancer patients and 137 "never-smoked" district controls were

estimated in Hong Kong to assess the possible causal relationship of passive smoking to lung cancer risk. When relative risks based on the husband's smoking habits, or lifetime estimates of total years, total hours, mean hours/day, or total cigarettes/day, or earlier age of initial exposure, were combined with years of exposure, there were no apparent increases in relative risk. However, when the data were segregated by histological type and location of the primary tumor, it was seen that peripheral tumors in the middle or lower lobes (or less strongly, squamous or small-cell tumors in the middle of lower lobes) had increasing relative risks that might indicate some association with passive smoking exposure."

A.21.2. Study Description

This study, the second of four from Hong Kong, is based on a secondary data set of reported female never-smokers. The parent study from which the data on ETS subjects was drawn includes ever-smokers in a matched case-control study of 200 cases and 200 controls (Koo et al., 1984; also see Koo et al., 1983). Its objective is to assess the role of passive smoking as a potential etiological factor in the high incidence rate of lung cancer among Chinese females in Hong Kong. The current article emphasizes the quantitation of lifetime ETS exposure and the histological profile of lung cancer in exposed never-smokers.

In the parent study, cases are from the wards or outpatient departments of eight hospitals in Hong Kong during 1981-83. Controls are healthy subjects from the community, matched on age (within 5 years), district of residence, and type of housing (public or private). The cases are incident, and control sampling is density. Attrition due to selection or follow-up totals 26 (8 too ill to interview and 18 with secondary lung cancers), leaving 200 cases for interview. Face-to-face interviews of 1.5 to 2 hours were conducted directly with cases and controls. There was no restriction of cases by cell type of lung cancer. The ETS subjects extracted from the parent study include 88 cases and 137 controls. Of the 88 cases, 83 were confirmed by histology and 5 were "confirmed malignant." The number of squamous cell and small cell cases combined is 32 (23 ETS exposed; 72%); the corresponding figure for adenocarcinoma and large cell combined is 44 (31 ETS exposed; 70%); 12 cases are of another cell type, or otherwise unspecified. For the 86 cases with available information, tumors were centrally located in 37 (25 ETS exposed; 67%) and peripherally in 46 (34 ETS exposed; 74%).

The term "never-smoker" applies to persons who have smoked a total of fewer than 20 cigarettes. Interview questions regarding exposure to ETS include cigarette and cigar smoking in the home during childhood, by the spouse and other cohabitants in adulthood, and workplace exposure. "ETS exposed" is technically used in several ways. For the comparison of exposed with

unexposed ever-marrieds, it means the husband ever smoked in the wife's presence. For measures of exposure in terms of duration or rate (e.g., total years, hours/day, total hours, and cig./day), there is some variation. For example, total years of exposure is derived by adding the years during which tobacco exposure occurred in the home or workplace. The total hours of exposure are calculated by multiplying the average hours per day of exposure by the years of exposure from each household smoker, or the amount of exposure at each workplace. The mean hours per day of exposure are found by adding the hours per day of home and workplace exposures and dividing this figure by the age of the subject. This figure is intended to approximate the average number of hours of exposure per day experienced by the subject, over her lifetime. Cumulative exposure is estimated by the total cigarettes smoked by family members, weighted by years of exposure.

When data are analyzed on the simple basis of whether a husband ever smoked in the presence of the wife, the crude and adjusted odds ratios are 1.55 (95% C.I. = 0.94-3.08) and 1.64 (95% C.I. = 0.87-3.09), respectively. The crude analysis applies to ever-marrieds only, which excludes three subjects. An adjusted analysis uses cigarettes per day smoked by the husband as the measure of ETS exposure. Conditional logistic regression was applied with stratification on district of residence and housing type (public/private); model parameters were included for age, family history of lung cancer (yes/no), number of live births, and number of years since exposure at home or in the workplace.

The crude and adjusted methods give very similar odds ratios and confidence intervals, but the tests for trend differ substantially. The test for trend on the crude data is based on the Mantel-Haenszel test, using midpoints of the intervals for cigarettes per day smoked by the husband; the significance value is $p = 0.10$. The p value for trend in the adjusted analysis is 0.32. For analysis of data by other measures of exposure, as described above, the estimated odds ratio ranges between 1.0 and 4.1 across the three levels of the various measures of ETS exposure for both the analyses of the crude data and the adjusted analyses by conditional logistic regression, with two exceptions from analysis of the crude data for hours per day of exposure. The results are not statistically significant in most cases, because the sample sizes at each exposure level are small. The dose-response patterns observed are clearly sensitive to the measure of ETS exposure used, with several exhibiting an apparent peak at a low exposure level. Although the authors acknowledge that it was troubling to find the lack of a response pattern, no further explanation is given.

The authors did not detect a significant trend in the crude or adjusted odds ratio for the four lifetime measures of passive smoking (total years, hours, mean hours/day, cig./day). Although the odds ratio for the intermediate level exposures of hours per day and cigarettes per

day was significant, the odds ratio at the highest levels of exposure for these two variables fell to a nonsignificant 1.0 to 1.2. In fact, the odds ratio for the highest exposure levels for three out of the four measurements were below all of those with lower exposures and ranged from a very weak 1.0 to 1.4. On the other hand, most of the crude and adjusted odds ratios were greater than 1.0. Measurements based on increasing intensity of exposure, defined as increasing years (or hours, or cig./day) by mean hours per day of exposure, also did not indicate a dose-response relationship. The analysis of total years of exposure with age of exposure did not suggest that earlier age of initial exposure and increasing years of exposure led to higher odds ratios.

It is concluded that when the lung tumors were segregated by histological type and location, the resulting analyses showed that peripheral tumors in the middle or lower lobes, and squamous or small cell tumors in the same lobes, exhibited better odds ratio patterns for passive smoking in terms of consistency, strength, and dose-response. The odds ratio for total years, hours, and hours per day measurements of squamous and small cell lung tumors indicated consistently elevated risks with increasing exposure. This pattern was not found for any of the adjusted odds ratios for adenocarcinoma or large cell lung cancers.

The cases are divided into two groups histologically, those with squamous cell or small cell tumors, and those with adenocarcinoma or large cell malignancies. Although none of the crude or adjusted analyses are found to be significant, it is concluded that an observed dose-response pattern seems to be more apparent in the squamous or small cell group. With regard to tumor location, some evidence suggests that peripheral tumors in the middle or lower lobes may be more common in passive smokers.

A.21.3. Comments

As described above, the data employed in the current study were taken from a larger retrospective study of female lung cancer in Hong Kong (Koo et al., 1984) that matched 200 cases and controls on age, district of residence and housing type (private or public, an indication of socioeconomic status). Attention to detail and accuracy is evident in most aspects of the parent study. In particular, considerable effort was put into attempting to ascertain a better quantitative measure of exposure than used in preceding studies of ETS. Records were apparently verified to the extent possible to cross-check the accuracy of information collected, cancers were verified histologically, and analyses investigated questions related to the histological types and sites of tumors that may be related to passive smoking.

The never-smokers from the parent study, 88 cases and 137 controls, compose the secondary data set on which the current article is based. The matching of the subjects, of course,

is no longer assured, leaving the comparability of the two groups uncertain. In addition, 60 (27%) of the subjects are widows, with no information provided on the distribution between cases and controls. Because spousal smoking is typically the variable on which ETS exposure pivots, this may have some bearing on the response. An adjustment is made in some analyses for years since exposure to cigarette smoke ceased, but no information is provided to describe or support the assumptions used to do that.

Some factors in the study itself may be contributing to the variable dose-response patterns. First, the number of ETS subjects is fairly small. When the subjects are classified into finer categories of exposure, the statistical variability is greatly increased (total cases and controls is below 60, on average). Second, questionable measurements of ETS may be causing some distortion. For instance, in the calculation of total years and total hours of ETS exposure, the years and hours were not added for simultaneous exposure to more than one smoker or for concurrent exposure in the home and workplace. Pipe smoking and the cigarette consumption levels of coworkers were excluded from the weighted average of the total cigarettes per day smoked by each household member. Additionally, the mean hours per day of exposure were derived by adding the hours per day of home and workplace exposures and dividing this figure by the *age* of the subjects. Thus, measurement appears to be based on the assumption that never-smoking women were exposed to ETS evenly throughout their lives (the authors claim that only subjects were used for which the exposure remained relatively regular during the lifetime, although no mention was found of cases being omitted because of failure to satisfy this criterion). Even if this assumption were valid, childhood and adulthood exposures are mixed as if the effects of exposure are interchangeable. Interestingly, differences between exposure in childhood and adulthood is one of the questions addressed in the article.

Although the objective is worthy, the attempt to quantitate exposure more precisely than previous studies appears to obscure more than to clarify. Assumptions are not made very explicit and their potential implications are not addressed well, which leaves some uneasiness about the conclusions. The authors have published at least three articles before this study that have some bearing on passive smoking and lung cancer, but their results are not discussed in the current study, even when the data analyzed are from the same source (Koo et al., 1983; Koo et al., 1984; Koo et al., 1985). Those articles, one of which describes the parent study (the 1984 citation), appear to reach somewhat different conclusions from this study regarding the predominance of histological type associated with passive smoking. Putting the current study's conclusions within the context of related prior work would enhance their clarity and interpretation.

Considering the reservations described above, the suggestion that the evidence indicates some association of passive smoking with the *location* of tumors is an overinterpretation of the data. A weaker conclusion is warranted, namely, that ETS exposure is associated with increased lung cancer incidence. What may be of most value in this study is the analysis based on the dichotomous classification of cases and controls as exposed or unexposed based on spousal smoking. Two concerns, however, will be reiterated. The ETS data are taken from a larger study not matched on smoking status, so they are unmatched. The study includes 80 widows, without mention of their distribution between cases and controls. In the adjusted analysis, an attempt is made to take into account the number of years since last exposure, which would require some assumption regarding the change of risk relative to cessation of exposure. Both of these concerns are mitigated, however, by the similarity of the odds ratios and confidence intervals for the unadjusted and adjusted analyses. The care and thoroughness of the study in general make the results on the odds ratio for exposure to spousal smoke a useful contribution for evaluation with other study outcomes.

A.22. LAMT

A.22.1. Author's Abstract

"In a case control study in Hong Kong, 445 cases of Chinese female lung cancer patients all confirmed pathologically were compared with 445 Chinese female healthy neighborhood controls matched for age. The predominant histological type was adenocarcinoma (47.2%). The relative risk (RR) in ever-smokers was 3.81 ($P<0.001$, 95% CI = 2.86, 5.08). The RRs were statistically significantly raised for all major cell types with significant trends between RR and amount of tobacco smoked daily. Among never smoking women, RR for passive smoking due to a smoking husband was 1.65 ($P<0.01$, 95% CI=1.16, 2.35), with a significant trend between RR and amount smoked by daily by the husband. When broken down by cell types the numbers were substantial only for adenocarcinoma (RR=2.12, $P<0.01$, 95% CI=1.32, 3.39) with a significant trend between RR and amount smoked daily by the husband. The results suggest that passive smoking is a risk factor for lung cancer, particularly adenocarcinoma in Hong Kong Chinese women who never smoked."

A.22.2. Study Description

This hospital-based case-control study was conducted in Hong Kong in 1983-86, to investigate whether smoking is a major risk factor for lung cancer in Hong Kong Chinese women and, if so, to determine the relationship between smoking and the histological types of lung

cancer. Both active and passive smoking are of interest. The ETS subjects constitute only a subset of the whole study, because it includes active smokers.

Eligible cases for the whole study are the 445 female patients with pathology-verified lung cancer admitted into eight large hospitals in Hong Kong during 1983-86. Cases were interviewed in person. Only a few eligible patients declined or were too ill to cooperate. An equal number of healthy neighborhood controls were identified and interviewed by density sampling. Controls were matched to cases on sex, age (± 5 years), and place of residence. The cases and controls include both never-smokers and ever-smokers, but smoking status was not used in matching. "Never-smoker" means a person who never smoked as much as one cigarette per day, or its equivalent, for as long as 1 year.

A woman is "ETS exposed" if her husband smoked for at least 1 year while they lived together. If the husband was an ever-smoker, information on the type of tobacco and amount usually smoked per day by the husband and the duration of exposure was obtained. No information was collected on ETS exposure from other household members' smoking or smokers at work. Single (never married) women were classified as nonexposed (6.8% and 5.2% in cases and controls, respectively). The treatment of widowed and divorced subjects is not explicitly addressed. Age and place of residence, as well as a series of other demographic variables, are similar between cases and controls.

The distribution of lung cancer by cell type in ETS cases is as follows: squamous cell, 12 out of 27 (number exposed/total); small cell, 6 out of 8; adenocarcinoma, 78 out of 131; large cell, 7 out of 9; and others or unspecified, 12 out of 24. The corresponding crude odds ratios and 95% confidence intervals are 0.85 (0.35-2.06), 3.00 (0.53-16.90), 2.12 (1.32-3.39), 3.11 (0.50-19.54), and 1.08 (0.41-2.82), respectively. The odds ratio for all cell types combined is 1.65 (1.16, 2.35), based on 115 out of 199 (exposed/total) cases and 152 out of 335 controls. The data for all cell types together, and for adenocarcinoma alone, are both significant at $p < 0.01$. No information is available on the airway proximity of tumors.

Trend tests were conducted for the amount smoked daily by the husband, categorized in terms of cigarettes as "nil," 1 to 10, 11 to 20, and 21 or more. The odds ratios in the three exposure categories are 2.18, 1.85, and 2.07, respectively, when all cell types are included. For adenocarcinoma alone, the corresponding odds ratios are slightly higher (2.46, 2.29, and 2.89). The dose-response relationship does not appear to increase between the lowest dose and the highest dose, but a test for trend is significant ($p < 0.01$ for all cell types and $p < 0.001$ for adenocarcinoma alone) when the "nil" group is included. No adjusted analyses are given.

The authors conclude that the significant trends observed between relative risk and amount smoked daily by husband, for all cell types combined and for adenocarcinoma alone supports the view that the observed association between ETS exposure and lung cancer is likely to be causal.

A.22.3. Comments

This study is the fourth of the Hong Kong epidemiologic inquiries into tobacco smoke as a possible etiological factor in the high rate of lung cancer, particularly adenocarcinoma, among women. Active smoking was included as well as passive smoking because the previous studies in Hong Kong were inconclusive. According to the authors, this led to the hypothesis that smoking is not a risk factor for adenocarcinoma in Hong Kong Chinese women. Matching of controls to cases was conducted for the whole study, including active smokers. It cannot be assumed, however, that the never-smokers alone, who constitute 45% of the cases and 76% of the controls, are matched.

Overall the study demonstrates care in planning and execution. The sample size of ETS subjects is moderately large, providing higher statistical power than the previous Hong Kong studies. All cases were pathologically confirmed as primary lung cancers, essentially eliminating the potential for error due to disease misclassification. Odds ratios were calculated by histological type for comparison. Cases and controls were interviewed personally, apparently with no proxy respondents and very few refusals, which reduces the potential for response bias. The exclusive use of incident cases helps to control potential selection bias, and density sampling of controls contributes to comparability of cases and controls. For the whole study, including smokers, healthy controls were matched to cases by sex, age, and neighborhood of residence. The mean and standard deviation of ages are nearly identical in cases and controls. According to the authors, a comparison by other demographic variables showed that, for the whole study, cases and controls were also comparable in place of birth, duration of stay in Hong Kong, level of education, marital status, and husband's occupation. Further attention to detail is evident in the clear definitions of "never-smoker" and "ETS exposure," essential to accurate classification of subjects for analysis and interpretation. Single women were treated as not exposed to husband's smoking, which could be a source of bias because these women may be exposed from other household members. This possibility was considered, however, because the article reports that similar results were obtained when single women were excluded.

In summary, the crude odds ratios vary between 2.1 and 3.1 for small cell carcinoma, adenocarcinoma, and large cell carcinoma, with adenocarcinoma significant at $p < 0.01$. The odds

ratios are consistently elevated at all three intensity levels of spousal smoking, varying between 1.8 and 2.9, with the odds ratio for adenocarcinoma alone somewhat higher than for all cell types combined. There is no apparent upward trend, however, from the lowest smoking intensity (1-10 cig./day) to the highest (21+ cig./day). These statistical results are ostensibly suggestive of an association between ETS exposure and lung cancer incidence, but they are based on only crude data with cases and controls unmatched, even on ages. Nor are statistical methods used that could adjust for matching variables, or other factors, in the data analysis (e.g., by stratification or logistic regression). Although this study was carefully conducted in most respects, the disregard for potential confounding effects leaves the authors' conclusion uncertain.

A.23. LAMW

(*Note:* This study is part of the thesis of LAM Wah Kit submitted to the University of Hong Kong for the M.D. degree in 1985, entitled "A Clinical and Epidemiological Study of Carcinoma in Hong Kong." The description given below is from Chapter 7 of the thesis only, entitled "Case-Control Study of Passive Smoking, Kerosene Stove Usage, and Home Incense Burning in Relation to Lung Cancer in Nonsmoking Females (1981-84)," which the author submitted in response to our request. The abstract below was prepared by the reviewers, since none was available from the author.)

A.23.1. Abstract

The study's objective is to investigate the hypothesis that an inhaled carcinogen may be related to the high incidence of centrally situated adenocarcinoma of the lung observed in nonsmoking female patients. Air pollution is probably not an important factor because it presumably affects both men and women. Most women in Hong Kong either stay at home or join the work force in commerce, services, or manufacturing, which are not associated with any known risk factor for lung cancer. Three etiological activities, all predominantly in the home, are considered in this study: passive smoking, kerosene stove cooking, and home incense burning. No evidence was found to implicate exposure to kerosene stove fumes or incense burning in centrally located adenocarcinoma. There is suggestive evidence of an association between ETS exposure from smoking husbands and occurrence of peripheral (but not central) adenocarcinoma. Why the location tends to be peripheral instead of central is speculative.

A.23.2. Study Description

(*Note:* The details of the study are not complete in the material provided. Some useful information, however, is available.)

The cases are all of the Chinese female patients admitted to the University Department of Medicine, Queen Mary Hospital, Hong Kong, between January 1981 and April 1984 with histologically and/or cytologically confirmed carcinoma of the lung of the four major cell types. Care was taken to exclude patients with secondary carcinoma of the lung; otherwise, all patients were included. The controls are Chinese female patients admitted to the orthopedic wards of the hospital in the period 1982-84, comparable to lung cancer patients in age and social class. Patients with pathological fractures due to smoking-related malignancies, or peripheral vascular disease-related orthopedic conditions were excluded.

Both cases and controls were patients of the third-class general wards, mostly from the lower income group. All subjects were interviewed in person. The questions covered dialect group, occupation, smoking habits, passive smoking, domestic cooking with kerosene, and home incense burning, in the form of a standardized questionnaire. For very ill patients, or for patients who spoke a dialect other than Cantonese or Mandarin, the next-of-kin was interviewed, with the patients as interpreter. The whole study, including active smokers, contains 161 cases and 185 controls, similar in age (median age is 67.5 [66] for cases [controls]), socioeconomic status (as measured by occupation and years of schooling), and recent residence. The author considered it unnecessary to stratify on these or any other variables.

The ETS subjects consist of 75 (144) cases (controls), including 16 (14) never-married cases (controls). The distribution of cases by cancer cell type is as follows: squamous cell (7), small cell (3), large cell (5), and adenocarcinoma (60). Questions related to ETS exposure include details on each smoker in the home (husband, others, mother, and father), amount smoked per day, hours of ETS exposure per day, and number of years smoked. Information about exposure in the workplace includes size of the workplace, number of coworkers who smoke, exposure time/day, and number of years of exposure at work.

Only the data for adenocarcinoma, the predominant cell type observed and the pathogenesis of interest, are analyzed. The number of cases is 37 out of 60 (exposed/total), and the number of controls is 64 out of 144, where ETS exposure refers to spousal smoking. The odds ratio (calculated by the reviewers) is 2.01 (95% C.I. = 1.09-3.72). The author divides the cases by location according to airway proximity, with 18 out of 32 (exposed/total) located centrally and 19 out of 28 in peripheral regions. The respective risk ratios are 1.61 and 2.64. Two tests were conducted for significance, including the Bayesian risk ratio analysis and a test of the slope for

the exposure parameter in a simple logistic regression model. The significance levels are 0.11 and 0.19, respectively, for the central location, and 0.01 and 0.02, respectively, for peripheral tumors. The test results differ widely for total passive smoking (home or workplace). For the central location, the respective significance levels are 0.09 and 0.3; for peripheral locations, the corresponding values are 0.03 and 0.15. It is suggested that the different outcomes for the two tests applied to total passive smoking may be due to a nonlinear logistic dose-response curve or to errors in assessing the level of exposure due to incomplete information. The apparent association between passive smoking and peripheral adenocarcinoma (and not central tumors) in the cases was unexpected. Based on the available raw data, exposure to a smoking spouse, cohabitant, and/or coworker is associated with an odds ratio of 2.51 (95% C.I. = 1.34-4.67) for all cell types combined. The author concludes that there is a suggestion of passive smoking associated with peripheral adenocarcinoma, particularly passive smoking attributable to smoking husbands. Kerosene and incense burning were not found to be associated with adenocarcinoma, either central or peripheral.

A.23.3. Comments

Cases and controls appear to be comparable in age, socioeconomic status, and recent residence for the whole study (including active smokers), although the study design is not matched on these or other variables. Some discrepancies between cases and controls are apparent, however, such as a higher percentage of cases than controls working outside the home (41% compared to 28%). The figures for nonsmokers alone (i.e., the ETS subjects) are not given, so comparability is uncertain for analysis of ETS exposure. Care has been taken to include only primary lung cancer patients among the cases, essentially eliminating this potential source of bias. Subjects were personally interviewed, with apparently only a small number of proxy respondents required, although no figure is given. The interviews were apparently not blinded, but that may have not been feasible considering the nature of the questions asked and the use of noncancer patients as controls. Considerable attention is given to histological type of cancer and the location in terms of airway proximity.

The author is particularly interested in the etiology of adenocarcinoma and focuses discussion on the adenocarcinoma cases to the exclusion of others. Although the raw data pertaining to other cell types are tabulated, more attention to those types in the analyses would have been useful. The adenocarcinoma cases are categorized further by central and peripheral location, which are analyzed separately. Again, a combined analysis would be useful (the reviewers calculated the crude odds ratio for the combined data, which is given above). Although

logistic regression is employed as one of the two statistical tools for analysis, factors that may differ between cases and controls are not included. Potential confounding variables need to be controlled for, by logistic regression, poststratification, or otherwise. To claim that cases and controls are similar in potential confounding characteristics does not alleviate the need to adjust for them in the analysis, particularly when the ETS data are a subset of the larger data set to which reference is made. Similarly, in testing three factors for an association with lung cancer (passive smoking, cooking with kerosene, and burning incense), it would be useful to conduct an analysis that will allow evaluation of the effect of each after adjustment for the other two.

The suggestive evidence that passive smoking is more likely associated with adenocarcinoma in peripheral rather than central locations may be logical but is weak, especially considering the lack of analytical rigor. The ratio of ETS-exposed cases of adenocarcinoma to the total is 18 out of 32 (56%) for central locations and 19 out of 28 (68%) for peripheral locations. This difference is not statistically significant ($p = 0.26$ by Fisher's exact test). Consequently, the "apparent association" between passive smoking and peripheral adenocarcinoma (and not central tumors) may well be due to chance alone. There is suggestive evidence in the data that passive smoking may be associated with lung cancer ($OR = 2.01$, $p < 0.03$ for a one-sided test), but that is based only on the crude odds ratio in unmatched data and needs to be confirmed by a more thorough evaluation of the data that takes potential confounders into account. Overall, this study provides some suggestive evidence for an association between passive smoking and lung cancer. Potential confounders (including age) have not been controlled for, however, so attribution of the elevated odds ratio to ETS exposure is uncertain.

A.24. LEE

A.24.1. Author's Abstract

"In the latter part of a large hospital case-control study of the relationship of type of cigarette smoked to risk of various smoking-associated diseases, patients answered questions on the smoking habits of their first spouse and on the extent of passive smoke exposure at home, at work, during travel and during leisure. In an extension of this study an attempt was made to obtain smoking habit data directly from the spouses of all lifelong non-smoking lung cancer cases and of two lifelong non-smoking matched controls for each case. The attempt was made regardless of whether the patients had answered passive smoking questions in hospital or not.

Amongst lifelong non-smokers, passive smoking was not associated with any significant increase in risk of lung cancer, chronic bronchitis, ischemic heart disease or stroke in any analysis.

Limitations of past studies on passive smoking are discussed and the need for further research underlined. From all the available evidence, it appears that any effect of passive smoke on risk of any of the major diseases that have been associated with active smoking is at most small, and may not exist at all."

A.24.2. Study Description

This study was undertaken in England, essentially from 1979-83. Its stated objective is to investigate the relationship between passive smoking and risk of lung cancer in nonsmokers. It is an outgrowth, however, of a hospital-based case-control study to assess whether the risk of cardiorespiratory disease associated with smoking varies by type of cigarette smoked. It was initiated in 1977 in 10 hospital regions in England. In 1979, interviewers began gathering information on passive smoking as well in four of the regions. Then in 1982, this case-control study of the effects of passive smoking was begun using nonsmoking cases identified by the ongoing cardiorespiratory effects study. For the new study, spouses of cases and specially selected controls were interviewed regarding smoking habits. Previously collected data on passive smoke exposure obtained from patients back to 1979 were used.

Basically, two substudies were conducted. One used the data obtained directly from hospitalized cases and controls to address several sources of passive smoke, including spousal (henceforward the "passive smoking" study); the second substudy used data obtained from the *spouses* of cases and controls along with corresponding information from the patients themselves, when available, to address spousal smoke exposure only (henceforward the "spousal smoking" study). Cases for the passive smoking substudy were currently married lifelong nonsmokers diagnosed with lung cancer (of any cell type), chronic bronchitis, ischemic heart disease, or stroke in one of four participating hospital regions. Controls were currently married lifelong nonsmoker inpatients diagnosed with a condition definitely or probably not related to smoking and individually matched on sex, age, hospital region, and, when possible, hospital ward and time of interview. Thus, density sampling was used when possible. For the spousal smoking substudy, previously married patients were excluded; the same criteria otherwise applied, except that controls were now matched on sex, age decade, and—as far as possible—hospital and time of interview.

Diagnoses were obtained from medical records. Exposure data were obtained through apparently unblinded, presumably face-to-face interviews with inpatients and their spouses. A total of 3,832 married cases and controls were interviewed regarding passive smoking through 1982; it is unclear how many potential subjects refused or died before interview. Only 56 of these

were married lung cancer cases meeting the spousal smoking study criteria. Spousal interview data were obtained for 34 of these cases and 80 controls; interviews were refused by the remainder. Although matching of cases and controls was initially carried out, it was not retained in the analysis, and no demographic comparison of cases and controls used in the analyses is provided. Diagnoses were apparently drawn from patients' charts, provisional diagnoses were used where no final diagnosis was specified, no data on diagnostic technique(s) or histology is presented, and no diagnostic verification is reported.

The patient population consists of never-smokers, defined as lifelong nonsmokers, which presumably excludes cigar and pipe smokers. Exposure to ETS is approached in several ways. The primary exposure is that of a spouse smoking manufactured cigarettes at some point over the course of a marriage. Spousal smoking in the 12 months before interview was also assessed. In addition, "regular" exposure to passive smoke in various situations (i.e., at home or work, during travel or leisure) was assessed. The first two exposures were quantified in numbers of cigarettes smoked per day, the others in terms of "not at all, a little, average, or a lot." Thus, it appears that cigar and pipe smoking may not have been included in the spousal smoking exposures. Comparison of individual responses regarding spousal smoking status by patients and their spouses revealed a high degree of concordance (97%) for smoking during the last 12 months and a substantial concordance (85%) for smoking during marriage. No other checks on exposure data were reported.

The ETS patient data set includes 56 cases and 112 controls who met the initial study criteria. Not all of these answered each passive exposure question, however, and not all met the criteria for the spousal interview study. Similarly, spouses of 34 cases and 80 controls provided exposure information of varying completeness. Thus the numbers involved in each analysis varied considerably. For smoking during marriage, data obtained directly from spouses indicated that for males and females combined, 24 of 34 lung cancer cases and 51 of 80 controls were exposed, which yields a crude odds ratio of 1.4 for spousal smoking. With standardization for age, an odds ratio of 1.33 (95% C.I. = 0.50-3.48) was reported. Data obtained from qualifying patients, in contrast, revealed 13 of 29 cases and 27 of 59 controls to be exposed, yielding a crude *and* adjusted odds ratio of 1.00 (95% C.I. = 0.41-2.44). Stratification by gender yielded adjusted odds ratios from spousal interview data of 1.60 (0.44-5.78) and 1.01 (0.23-4.41) for females and males, respectively, with corresponding odds ratios from patient interview data of 0.75 (0.24-2.40) and 1.5 (0.37-6.34). When spouses identified as smokers by interview with either source were classified as exposed, an odds ratio of 1.00 (0.37-2.71) was obtained for female subjects. For the larger inpatient passive smoking study population, age-standardized odds ratios for passive smoke

exposure at home, at work, during travel, and during leisure revealed no consistent associations, with as many negative as positive relationships observed after adjustment for both age and whether still currently married. The same inconsistency held true for spousal smoking during the last 12 months and during the whole marriage. Adjustment for working in a dusty job reportedly did not affect the conclusion that passive smoking was not associated with risk.

Spousal smoking was slightly negatively associated with chronic bronchitis, ischemic heart disease, and stroke, whereas a combined ETS exposure index was negatively associated with heart disease but positively associated with bronchitis and stroke.

The author concluded that the findings appear consistent with the general view, based on all the available evidence, that any effect of passive smoking on risk of lung cancer or other smoking-associated diseases is at most quite small, if it exists at all. The marked increases in risk noted in some studies are more likely to be a result of bias in the study design than of a true effect of passive smoking.

A.24.3. Comments

The heart of this study is the spousal interview investigation of lung cancer and spousal smoking. Only 34 case spouses and 80 control spouses, and even fewer of the corresponding cases and controls themselves, are included, which gives the study low statistical power. Because the study began with hospital inpatient married lifelong nonsmokers, and matching on several key factors was employed, good comparability of cases and controls would seem readily achievable. No case-control demographics are provided, however, and matching is abandoned in the analyses. Undoubtedly, the high rate of refusals and frequency of omitted responses (themselves a potential source of selection and information bias) contributed to the decision to abandon matching, with the aim of preventing further substantial reduction in numbers through exclusion of unmatched subjects. The unfortunate result is that the comparability of the cases and controls is uncertain. At least all are drawn from the same four hospital areas within a fairly limited timespan, which, in combination with the other study criteria, reduces the likelihood of serious noncomparability.

Numerous opportunities for misclassification of disease and exposure status are present. Current working diagnoses are apparently drawn from patient charts without verification, and controls are selected from patients with diagnoses judged either probably or definitely not associated with smoking by unspecified criteria. This creates considerable potential for misclassification, both through inaccuracies in diagnoses generally and through inclusion of smoking-related diseases in the control group particularly, which would produce a downward bias in results. Exposure misreporting and recall problems would seem least likely where spouses are

interviewed directly about exposure within the last 12 months. Results for this situation are not presented, although they are reportedly similar to those for smoking during marriage.

The larger inpatient study elicited smoking data from patients, and only for their *first* spouse for patients who had remarried; thus, exposure occurring in subsequent marriages is not addressed. In addition, no information on duration or level of smoking in marriage is used in any of the spousal smoking analyses. The most likely result of these problems is nondifferential misclassification resulting in a bias toward the null. For general estimated home, work, travel, or leisure exposure to passive smoke, rough quantification *is* attempted by having patients categorize their exposure as "not at all, a little, average, or a lot." By necessity, this is a very subjective evaluation, and people more acclimated to smoke and tolerant of exposure might well tend to characterize a given amount of exposure as less severe than would a person of less tolerance who more actively avoids exposure. This tendency would produce a bias toward negative association.

Standardization for age and restriction of cases and controls to currently married lifelong nonsmokers should control potential confounding by age, marital status, or active smoking, although misreporting of current or former active smoking cannot be ruled out entirely. Dusty occupation reportedly had no effect on the larger inpatient study results. Potential confounding by race, socioeconomic status, diet, cooking habits, or any additional factors was not addressed.

One might expect the most accurate reporting of spousal smoke exposure when spouses are interviewed directly regarding their own smoking habits, and the most inadvertent misclassification when patients are queried about the smoking status of their first marital partner only. Analyses along these lines yielded slightly positive associations with smoking for the former and negative with the latter approach. No consistent pattern of association was seen for other sources and lung cancer, although high combined exposure scores were associated positively with chronic bronchitis and stroke and negatively with ischemic heart disease.

In summary, this study presents equivocal results that neither strongly confirm nor refute the hypothesis that passive smoking mildly increases risk of lung cancer. The quality of the study, however, is a limitation. The discrepant results for subject-supplied data (OR = 0.75) and spouse-supplied data (OR = 1.60), varying degrees of completeness of information on subjects, the subjective nature of questions regarding ETS exposure, and lack of information on intensity or duration of husband's smoking do little to inspire confidence in the study's data and, consequently, the results from analysis of those data.

A.25. LIU

A.25.1. Author's Abstract

"In Xuanwei County, Yunnan Province, lung cancer mortality rates are among the highest in China in both males and females. Previous studies have shown a strong association of lung cancer mortality with indoor air pollution from 'smoky' coal combustion. In the present case-control study, 110 newly-diagnosed lung cancer patients and 426 controls were matched with respect to age, sex, occupation (all subjects were farmers), and village of residence (which provided matching with respect to fuel use). This design allowed assessment of known and suspected lung cancer risk factors other than those mentioned above. Data from males and females were analyzed by conditional logistic regression. In females who do not smoke, the presence of lung cancer was statistically significantly associated with chronic bronchitis (odds ratio [OR] = 7.37, 95% confidence interval [CI]: 2.40-22.66) and family history of lung cancer (OR 4.18, 95% CI: 1.61-10.85). Females' results also suggested an association of lung cancer with duration of cooking food (OR 1.00, 9.18 and 14.70), but not with passive smoking (OR 0.77, 95% CI: 0.30-1.96). In males, lung cancer was significantly associated with chronic bronchitis (OR 7.32, 95% CI: 2.86-20.18), family history of lung cancer (OR 3.78, 95% CI: 1.70-8.42), and personal history of cooking food (OR 3.36, 95% CI: 1.27-8.88). In males a dose-response relationship of lung cancer with smoking index (years of smoking/amount of smoking) was shown by risks of 1.00, 2.61, 2.17 and 4.70."

A.25.2. Study Description

This study was undertaken in Xuanwei county of China's Yunnan Province, a county whose lung cancer mortality rates are among the country's highest and wherein burning of smoky coal indoors in unventilated pits is a common practice. The study sought to assess "the influence of factors other than type of fuel on the occurrence of lung cancer in Xuanwei."

Cases of newly diagnosed lung cancer occurring among farmers at hospitals and clinics in Xuanwei between November 1985 and December 1986 were identified as potential study subjects. Up to five controls were identified for each case, depending on availability after matching on age ($\pm$ 2 years), gender, and village of residence. A total of 112 cases were identified, from which 2 were excluded due to unknown addresses. Of 452 candidate controls, 26 were excluded due to erroneous questionnaire responses. All subjects were interviewed face-to-face by trained personnel using a standardized questionnaire, and blinding extended to both interviewers and interviewees.

The final study groups consist of 54 (56) female (male) cases and 202 (224) female (male) controls. Mean age is 52 years for both cases and controls, who are also similar in family size, ethnicity, birthplace, dwelling type, and type of fuel used (smoky coal, wood). Separate breakdowns for males and females are not provided. Very few of the cases (19/110 = 17%) were histologically or cytologically diagnosed, and no verification of diagnosis or exclusion of secondary tumors was undertaken (except to monitor mortality among some of the cases).

Exposure to ETS was not evaluated for males. Among females, only one subject (a control) reported ever having smoked, so the ETS population of females effectively consists of never-smokers. Subjects were classified as exposed to ETS if their household contained at least one smoker. Exposure is not quantified, and it is unclear whether former or only current exposure is intended. No checks on exposure status or consideration of marital status are mentioned, and no histological data are presented.

The ratio of exposed to unexposed female subjects is 45 out of 94 (176/202) for cases (controls), yielding a crude odds ratio of 0.74. A conditional logistic regression analysis adjusted for other risk factors (presumably the other factors referred to are age-began-cooking and years-of-cooking) gives an odds ratio of 0.77 (95% C.I. = 0.30-1.96). No further analyses of ETS exposure are provided.

Four non-ETS factors are significantly associated with lung cancer among females: family history of lung cancer (OR = 4.18; 95% C.I. = 1.61-10.85), personal history of bronchitis (OR = 7.37; C.I. = 2.40-22.66), age-began-cooking (OR = 2.44-1.03, but with a reversing and nonsignificant dose-response), and years-of-cooking (OR = 2.49-2.25, nonsignificant trend). Among males, significant positive associations were noted for total smoking index, often-cooking-own-food, family history of lung cancer, and history of chronic bronchitis, whereas age-began-smoking, years of smoking, and intensity of smoking showed modest but nonsignificant associations with lung cancer.

The authors conclude that "it is quite conceivable that the large amount of air pollutants inhaled during indoor smoky coal burning in Xuanwei partly overwhelm the carcinogenic effect of tobacco smoking" and "may also overwhelm the carcinogenic effect of passive smoking." "Our results disclose important associations of lung cancer with factors other than fuel type and therefore indicate that those factors must be considered in any comprehensive, quantitative risk assessment of lung cancer in Xuanwei. Our results also confirm indirectly that smoky coal pollution is an important determinant of lung cancer in Xuanwei."

A.25.3. Comments

This modestly sized study was not designed to test for effects of ETS exposure. Rather, it is an hypothesis-generating exercise aimed at covering a broad range of possible risk factors. Within that context, the study has considerable merit, but as an investigation of ETS it has numerous flaws.

Restriction to farmers minimizes concerns with occupation and overall lifestyle, and control selection, including matching on age, gender, and village, produced demographically comparable case and control populations for males and females combined despite the enigmatic exclusion criterion for controls. It is unknown, however, whether the groups remain comparable after subdivision into males and females.

The use of newly diagnosed cases reduces potential selection bias due to inclusion of prevalent cases, but the heavy reliance (83%) on clinical and radiological diagnosis and the absence of independent confirmation or exclusion of secondary tumors introduces a strong potential for misclassification of disease and precludes analyses by cell type. The observation that follow-up of a number of lung cancer patients revealed that almost all died within 6 months of diagnosis does little to confirm diagnostic validity, contrary to the authors' interpretation. Such presumably random misclassification would make detection of an existing ETS-lung cancer association more difficult.

Exposure data collection procedures, particularly the exclusive use of face-to-face interviews without resort to proxies and the blinding of both interviewers and subjects, are laudable. For ETS, however, the exposure measure used is nonspecific and nonquantitative. Complications due to past exposure and differences in degree or duration could distort the observed disease-exposure relationship, probably biasing results toward no effect.

Potential confounding is not adequately addressed in the statistical analysis. The authors are particularly concerned with indoor smoky coal burning due to the known strong correlation between smoky coal use and lung cancer mortality in Xuanwei. Wishing to focus their investigations on factors other than smoky coal, they matched cases and controls on village, which "provided effective matching on fuel type." But because age and a host of other demographic factors, as well as smoky coal consumption, were comparably distributed in cases and controls (see Study Description), these factors were not considered further in the data analysis. This is a serious flaw, for pair matching was not retained in the analysis; thus, none of the above factors is effectively controlled for. The conditional regression analyses do control for risk factors other than those cited above, but exclusion of age, fuel type (e.g., smoky coal), and degree of exposure to fuel fumes may produce misleading results.

The presence of other significant risk factors for lung cancer makes detection of an effect from ETS, if present, less likely. Masking by the presence of smoky coal and other factors in the study environment is probably a factor in the remarkably weak association between active smoking and lung cancer among study males (adjusted OR = 1.36). If even an effect of active smoking remains largely obscured under study conditions, it is unlikely that an effect of ETS would be detected.

Overall, this study makes important contributions to its principal objectives but is not helpful in assessing ETS and lung cancer. It is observed, for example, that persons in areas of Xuanwei with high lung cancer rates (and high smoky coal consumption) may inhale more BAP (benzo-[a]-pyrene) by spending 8 hours indoors than by smoking 20 cigarettes. Due to such factors, the authors observe, "the effect of passive smoking on lung cancer may depend on local environmental factors and results obtained in a given region may therefore not be applicable to other regions." Avoidance of areas atypically rich in competing exposures and careful control of potential confounders and interactive risk factors must be key objectives in studies of ETS and lung cancer.

A.26. PERS

A.26.1. Author's Abstract

"The relation between passive smoking and lung cancer was examined by means of a case-control study in a cohort of 27,409 nonsmoking Swedish women identified from questionnaires mailed in 1961 and 1963. A total of 77 cases of primary carcinoma of the bronchus or lung were found in a follow-up of the cohort through 1980. A new questionnaire in 1984 provided information on smoking by study subjects and their spouses as well as on potential confounding factors. The study revealed a relative risk of 3.3, constituting a statistically significant increase ($p < 0.05$) for squamous cell and small cell carcinomas in women married to smokers and a positive dose-response relation. No consistent effect could be seen for other histologic types, indicating that passive smoking is related primarily to those forms of lung cancer which slow the highest relative risks in smokers."

A.26.2. Study Description

This case-control study, undertaken to explore the role of passive smoking in lung cancer, is based on cohorts of Swedish women assembled prior to 1963. Nonsmokers were drawn from these cohorts to create matched case and control groups.

Cases are nonsmoking Swedish women included in the Swedish National Census or Twin Registry who responded to smoking status questionnaires in 1961-63 and who subsequently developed primary lung or bronchial cancer by 1980. Two control groups were cumulatively sampled from National Census or Twin Registry subjects who did not develop lung or bronchial cancer. In group 1, two controls were matched to each case on year of birth (± 1 year). In group 2, two controls were matched to each case (2:1) on year of birth (± 1 year) and vital status in 1980. Thus, there were 58 cases and 232 controls from the National Census and 34 cases and 136 controls from the Twin Registry. A follow-up questionnaire that included questions on spousal and parental smoking habits was distributed to each subject or the next-of-kin in 1984. Out of 92 cases of tracheal, bronchial, lung, or pleural cancer occurring by 1980, 15 cases in which a diagnosis of primary cancer of the lung or bronchus was not established were excluded. Exclusion of women indicated to be active smokers according to the 1984 questionnaire, or for whom ETS exposure information was not available, eliminated a further 10 cases. Active smoking and lack of exposure information eliminated 21 of the 368 controls initially assembled. Histological confirmation was available for 64 of the 77 cases with primary lung or bronchial cancer; 12 cases were cytologically confirmed; and the remaining case was verified at autopsy.

Never-smokers are subjects who report that they have never smoked any form of tobacco. A woman is ETS-exposed if she has ever been married to a tobacco smoker; for women married more than once, only the longest marriage is considered. Exposure to spousal smoking is quantified in units of cigarettes per day or packs of pipe tobacco per week; parental smoke exposure is defined as 0, 1, 2, etc. (equal to the number of parents who smoke). No other sources of ETS exposure are considered. Never-smoking status was checked by comparing the responses to the 1961-63 questionnaires with those obtained in 1984. Data on sources of ETS were not checked. Never-married women were classified as nonexposed to spousal smoke; widows and divorcees were classified according to the smoking status of the former husband with whom they had lived the longest. Of the never-smoking cases for whom passive smoking information was available, squamous and small cell tumors constituted 20 cases, 13 of whom were exposed to spousal smoke; of the other 47 cases, 20 were exposed to spousal smoke.

Responses to the ETS questionnaire were available for a total of 81 never-smoking cases and 347 never-smoking controls. The 67 cases with primary lung or bronchial cancer constitute the ETS study subjects. It is not clear how many of the 347 potential controls were employed in each analysis. Presumably many (up to 4 for each excluded case from the original 81 never-smoking cases) were not used in the matched analysis, whereas most or all were used in the unmatched analyses described subsequently.

A total of 33 of the 67 cases were exposed to spousal smoking. Among the never-smoking women, matched analyses indicate that the odds ratio for marriage to a smoker is 3.8 (95% C.I. = 1.1-16.9) for squamous or small cell cancer compared to control group 1, 3.4 (0.8-20.1) compared to control group 2, and 3.3 (1.1-11.4) compared to both groups combined. For other cell types, corresponding odds ratios are 0.7, 0.8, and 0.8, respectively. Subsequent analyses abandoned matching and pooled all controls. For squamous and small cell cancer, high exposure to spousal smoking (15 or more cig./day or at least one pack of pipe tobacco/week for 30+ years) is associated with an age-adjusted odds ratio of 6.4 (1.1-34.7), whereas the lower exposure is associated with an odds ratio of 1.8 (0.6-5.3). The estimated odds ratios for other types of cancer are also elevated for the higher exposure, but not at the lower one. Odds ratios adjusted for age and spousal smoking when at least one parent smokes as well are above 1 (1.9; 95% C.I. = 0.5-6.2) for squamous and small cell types but not for other types.

Logistic regression analyses reportedly produced the same results as did the stratified analyses. In addition, occupation, household radon, and urban or rural status had no significant effect. It is notable, however, that for all cancers combined, the odds ratio for radon exposure is 1.4 (0.4-5.4), the odds ratio for spousal smoking is 1.2 (0.6-2.6), and the odds ratio for radon and spousal smoking combined is 2.5 (0.8-8.5). No separate analyses for squamous and small cell cancer are provided for radon and other potential confounders. The authors conclude that exposure to ETS is related primarily to the forms of lung cancer that show the highest relative risks in smokers. The results are internally consistent.

A.26.3. Comments

Although based on cohorts assembled for other purposes, this case-control study was specifically designed to investigate passive smoke exposure. Thus, all participants are ETS subjects, which are matched. Matching criteria are rather modest—birthdate (± 1 year) for control group 1 and birthdate and vital status for control group 2. Because the study targeted *all* cases detected in the same cohorts from which matching controls were randomly drawn, good comparability of cases and controls is likely. No demographic comparisons of cases and controls for whom ETS information was available—and thus who constituted the analytical subjects—were provided to confirm this, however. Data on active smoking among subjects were collected both at the start and after the end of mortality monitoring, providing an opportunity to verify the nonsmoking status over time and exclude individuals whose status had changed (apparently those reported in 1984 to have smoked daily for at least 2 years were so excluded). Thus, the probability of significant misclassification of active smoking status is low. Data on passive

smoking were collected only after the end of mortality monitoring and by necessity employed proxy respondents extensively, so some misclassification of exposure is likely. Self-administration of questionnaires eliminates interviewer bias as a source of error, making misclassification less likely to be systematic, but preferential recall of smoke exposure by relatives of cancer victims could have produced a bias. Misclassification of disease is unlikely to have been a problem because most cases were histologically diagnosed and secondary lung cancers were excluded.

Consideration of spousal smoke exposure only in their longest marriage among women married more than once means that some of the unexposed group probably had substantial exposure to spousal smoking, creating a bias toward no association. Classification of all never-married women as unexposed despite possible smoking by cohabitants creates the same bias. Few subjects (less than 20%) were single, but the frequency of remarriage is unknown; therefore, it is unclear how important this bias might have been. Lack of consideration of workplace smoke exposure may also have contributed a bias toward the null hypothesis of no association.

The authors addressed a number of potential confounders. Restriction of subjects to women eliminates potential confounding by gender, and age is addressed by retaining age-matching or, alternatively, adjusting for age in all analyses. Reportedly neither occupation, radon, nor urban residence had significant confounding effects, which makes confounding by other factors related to socioeconomic status or lifestyle unlikely, too. An analyses of parental smoking controlled for spousal smoking. The authors do, however, present evidence that the odds ratio for simultaneous exposure to radon and spousal smoke approximately equals the sum of the separate odds ratios for radon and spousal smoke, consistent with additivity of the effects. But, perhaps due to limited numbers, they report results only for all cancers combined rather than for the squamous and small cell subgroup in which the only *significant* spousal smoking association was observed.

In summary, this study reports a consistent, dose-related, and (for high exposure levels) statistically significant positive association between exposure to spousal tobacco smoke and squamous and small cell carcinoma of the lung; a positive but nonsignificant association was also observed for parental smoke exposure. No significant associations were observed for other cell types. The observed associations apparently are not due to confounding by other major risk factors, although dietary and smoking habits were not directly addressed. A possible recall bias cannot be ruled out but seems unlikely given the negative results obtained for cancers other than squamous and small cell. The study provides a useful contribution to investigation of the relationship between ETS exposure and lung cancer.

A.27. SHIM

A.27.1. Author's Abstract

"A case-control study of Japanese women in Nagoya was conducted to investigate the significance of passive smoking and other factors in relation to the etiology of female lung cancer. A total of 90 nonsmoking patients with primary lung cancer and their age- and hospital-matched female controls were asked to fill in a questionnaire in the hospital. Elevated relative risk (RR) of lung cancer was observed for passive smoking from mother (RR=4.0; $p<0.05$) and from husband's father (RR=3.2; $p<0.05$). No association was observed between the risk of lung cancer and smoking of husband or passive smoke exposure at work. Occupational exposure to iron or other metals also showed high risk (RR=4.8; $p<0.05$). No appreciable differences in food intakes were observed between cases and controls."

A.27.2. Study Description

This study was undertaken in Nagoya, Japan, during 1982-85 to investigate the significance of passive smoking and other factors such as occupational history, domestic heating system, and dietary habits in the etiology of lung cancer in nonsmoking Japanese women. All data were collected specifically for this study, which was limited to never-smokers.

All subjects were obtained from four hospitals in Nagoya. Cases are women with primary lung cancer (of any type) treated in these hospitals between August 1982 and July 1985 who reported themselves to be never-smokers and consented to interview. Controls are women with a diagnosis other than lung cancer from the same or adjacent wards with controls matched 2:1 with cases on age (± 1 year), hospital, and date of admission. Cases were not restricted to incident disease, but controls were essentially density-sampled by admission date. Data collection was by self-administered questionnaire; no attempt at blinding is described. Of 118 female lung cancer cases treated during the study period, four refused to participate in the study and 24 were excluded as current or former smokers. Only a single matching control could be found for 17 of the cases. No other information on loss of potential controls is provided. There is a total of 90 (163) cases (controls), with 52 (91) currently married to a smoker. Cases and controls share identical age ranges (35-81 years) and have nearly identical mean ages (59 years for cases, 58 for controls). All cases were histologically diagnosed, excluding secondary lung cancers.

All study subjects are self-reported never-smokers. A number of individual sources of ETS in the home are considered, including smoking by mother, father, husband, father-in-law, mother-in-law, offspring, and siblings. For each of these sources, smoking in the home at any time constituted exposure. Workplace exposure was characterized simply as presence or absence;

for other exposures, the number of cigarettes per day was obtained. In addition, data on length of marriage, time spent in the same room as the wife, and total number of cigarettes smoked were obtained for husbands. Exposure data were not checked, and marital status was not considered in the design or analysis of the study. The predominant type of lung cancer is adenocarcinoma (69 out of 90 cases), followed by squamous (13), large cell (4), small cell (3), and adenoid cystic carcinoma (1). No data on airway proximity are provided.

Logistic regression was used to estimate the relative risk for each source of ETS exposure. No significant association with lung cancer was noted for smoking by the husband (RR = 1.1), father (RR = 1.1), husband's mother (RR = 0.8), offspring (RR = 0.8), or siblings (RR = 0.8); smoking by the subject's mother (RR = 4.0) and by the husband's father (RR = 3.2), however, are significant ($p < 0.05$). None of eight dietary factors, including green-yellow vegetable and fruit intake, demonstrated a significant association, nor did type of cooking fuel or frequency of cooking oil use. Occupational history of exposure to iron or other metals shows a moderately strong but nonsignificant association (RR = 2.8), whereas for use of kerosene, coal, or charcoal heating there is a mild association (RR = 1.6-1.7).

Simultaneous stratification by father-in-law's and mother's smoking indicates that the effects of the two exposures are not additive. Smoking by father-in-law, smoking by mother, and occupational metal exposure were included simultaneously in a logistic regression model. After adjusting the effect of each variable for the other two, the relative risk for maternal smoking, father-in-law's smoking, and metal exposure are 2.1, 3.2 ($p < 0.05$), and 2.4, respectively. The authors conclude that the exposure to tobacco smoke from household members (i.e., mother or husband's father) could be associated with female lung cancer. As the precise situation of passive smoking in the home or other places is still unclear, however, they find that further studies are needed to clarify the significance of passive smoking in relation to the etiology of lung cancer in Japanese women.

A.27.3. Comments

This study employs a moderate number of well-matched cases and controls. Their comparability appears good, as supported by the identical age ranges and similar mean age and occupational categories for the two groups. A further strength of the study is its lack of reliance on proxy information with attendant potential for inaccurate recall. Exposure information was obtained from self-administered questionnaires, which eliminates the possibility of interviewer bias but may lead to inaccuracy due to misinterpretation of questions or varying care in their completion. Such problems with exposure information would tend to mask any actual association.

Lung cancer was histologically diagnosed in all subjects and secondary lung cancers excluded, so diagnostic accuracy appears good for cases. Control diagnoses, however, were not validated, so some smoking-related disorders (in addition to the heart conditions noted in 3% of controls) may be included among the controls, a problem that once again would tend to reduce any observed association.

Restriction of subjects to never-smokers maximizes efficiency because effects of passive smoking would likely be dwarfed by active smoking. But it is unclear precisely what subjects were asked about their smoking status. Were any cut-points regarding pack-years or cigarettes per day specified? Was former smoking specifically questioned? Thus, some misclassification of smoking status may have occurred, and if a greater proportion of persons with smoking family members misreport themselves to be never-smokers, this would create an upward bias.

The authors restrict their assessment of exposure from relatives to at-home smoking, which may be more meaningful than total smoking as a potential source of passive smoke exposure. Furthermore, they collected data on smoking habits of all relatives, not just spouses or parents, thus reducing the chance of missing an exposure source. On the other hand, there is no consideration of total household smoking (all sources combined), cumulative exposure (except for husbands), or of pipe or cigar smoking; nor is there differentiation of current and former exposure--all potential sources of exposure misclassification, which would tend to make an association more difficult to detect.

Of the several sources of ETS exposure at home, only the relative risks for smoking by the mother and by the father-in-law are suggestive, and both of these are significant ($p < 0.05$). When these sources are considered simultaneously, however, and the effect of each is adjusted for the other, smoking by the husband's father remains significant ($RR = 3.2$; $p < 0.05$) but the effect of mother's smoking is diminished ($RR = 2.1$) and is not statistically significant. The authors' emphasis on the significance of exposure in childhood from maternal smoking appears misplaced. Exposure from the father-in-law is, of course, in adulthood. There is no evidence of an effect from husband's smoking ($RR = 1.1$), however, and these exposure sources were considered simultaneously so that the effect of one could be adjusted for the other. The large number of comparisons (e.g., eight groupings of passive smoke exposure, alternative spousal exposure measures, and several occupational and eight dietary factors) increases the likelihood that an observed relative risk will appear to be significant by chance alone (the effect of multiple comparisons).

Another aspect of the statistical analysis worth noting is that, although cases and controls appear well matched on age, hospital, and hospital admission date, these factors and other

potential confounders are not included in an adjusted analyses of the data (aside from the example with three sources of exposure described above). Consequently, possible confounding cannot be ruled out, although the demographic similarities between cases and controls make severe confounding less likely.

In summary, this study presents some interesting results. It finds a strong (adjusted RR = 3.2) and statistically significant association between father-in-law's smoking at home and lung cancer and associations for maternal smoking and occupational metal exposure as well. The lack of association for any of the other sources of ETS examined could be due to problems with exposure assessment and control disease criteria. Equally, however, given the unclear treatment of matching factors in the analysis, and the number of variables explored, the few substantial associations noted might be due to chance, confounding, or both. Were potential confounders clearly treated in their analyses, this study would have made a stronger contribution. As it stands, the study's data are of moderate utility, providing the number of comparisons and limitations regarding bias are kept in mind.

A.28. SOBU

A.28.1. Author's Abstract

"A hospital-based case-control study among non-smoking women was conducted to clarify risk factors in non-smoking females in Japan. Cases consisted of 144 non-smoking female lung cancer patients, and these were compared to 713 non-smoking female controls. The odds ratios (95% confidence interval) for use of wood or straw as cooking fuels when subjects were 30 years old was estimated as 1.77 (1.08 to 2.91). For those whose household members, other than husbands, had smoked, the odds ratio was estimated as 1.50 (1.01 to 2.32). For those whose mothers had smoked, the odds ratio was estimated as 1.28 (0.71 to 2.31). Use of heating appliances did not show an elevated risk. Some points to be noted in this study of low-risk agents for lung cancer are discussed."

A.28.2. Study Description

This study was conducted in Osaka, Japan, to clarify risk factors for lung cancer in nonsmoking females in Japan. Of interest are the roles of both active and passive smoking and other indoor air pollutants, particularly smoke or fumes from sources of indoor cooking and heating. This article reports only on female nonsmokers in the study, which is not matched on any variables. A very similar article presenting interim results and using slightly fewer subjects than the one described here is by Sobue and coworkers (1990).

Cases consist of all newly admitted lung cancer patients in eight Osaka hospitals between January 1986 and December 1988. Controls were collected from newly admitted patients in one or two other wards of the same hospitals during that period. Almost 90% of the controls were admitted as cancer patients, about half of which were diagnosed with breast cancer. Self-administered questionnaires designed for this study were completed by both cases and controls at the time of hospital admission. Cases are incident and control sampling is density, unmatched aside from the time of hospital admission (within 1.5 years). The entire study, including active smokers and males, consists of 295 (1,079) female (male) cases and 1,073 (1,369) female (male) controls. Nonsmoking females compose 156 cases, of which there was missing information on 12. The resultant number of ETS subjects is 144 (731) female nonsmoking cases (controls). The age distribution of the cases (controls) is as follows: 40 to 49, 20 (238); 50 to 59, 34 (229); 60 to 69, 41 (186); and 70 to 79, 34 (78). The corresponding percentages are 14 (33), 34 (31), 28 (25), and 24 (11), which indicates that controls tend to be younger than cases. Also, the mean age of cases (controls) is 60 (56). There was no systematic review of histological diagnosis. All original diagnoses were confirmed microscopically, however, and all the pathologists involved in the eight participating hospitals were experienced specialists in lung cancer. Thus, the likelihood of secondary lung cancers among the cases should be small.

Several sources of ETS exposure are included, all of which occur in the home. Exposure in adulthood is expressed by two measures--smoking by the husband and by other household members (the last category consists chiefly of households where the husband's father and/or sons smoke). Three sources of exposure in childhood are considered--father smokes, mother smokes, and other household members smoke. No information is provided on how exposure to spousal smoking is handled for unmarried women (single, divorced, or separated). The entire complement of cases and controls is included in the summary data for each of the five sources of exposure given above. If only married women were included in the study, no mention of it was found.

The histological data for ETS subjects are not classified by exposure to ETS, but the percentage of cases by cell type are given: squamous cell (8), small cell (5), adenocarcinoma (78), large cell (5), and other (4). The ETS data on spousal smoking consists of 80 out of 144 (exposed/total) cases and 395 out of 731 controls, for an odds ratio of 1.13 (95% C.I. = 0.78-1.63). (Our calculations give 1.06 [0.74-1.52].) The odds ratio for ETS exposure from other household members in adulthood is 1.57 (95% C.I. = 1.07-2.31). (Our calculated values are 1.77 [1.21-2.58].) For ETS exposure in childhood by the father, by the mother, and by other household members, the respective odds ratios are 0.79 (95% C.I. = 0.52-1.21), 1.33 (95% C.I. = 0.74-2.37), and 1.18 (95% C.I. = 0.76-1.84). Tests were conducted by the Mantel-Haenszel procedure, with

stratification by age and education (two levels). Analysis by logistic regression, adjusted for age at time of hospitalization, was conducted for two of the exposure measures described above with similar outcomes. Based on this evidence, the author concludes that for childhood exposure, a slight increase of risk was suggested for those with smoking mothers, although statistical significance was not observed. For exposure in adulthood, an elevated risk was estimated for those with smoking household members other than husbands.

The statistical analysis includes exposure to sources other than ETS, namely, the use of wood or straw as cooking fuel, the use of heating equipment that pollutes the room with combustion products, and the use of charcoal foot warmers. All exposures considered, including ETS, are smoke or fumes from products burned indoors. It is concluded that significantly elevated risks were observed for subjects who had used wood or straw as cooking fuels at 30 years of age (OR = 1.89; 95% C.I. = 1.16-3.06). No elevated risks were found for sources of indoor heating (use of kerosene, gas, coal, charcoal, and wood stoves without chimneys). Similarly, no significance was found for the use of charcoal foot warmers, a practice that was popular until the 1960's.

A.28.3. Comments

With 144 cases and 731 controls, the sample size is larger than many of the other case-control studies on ETS. Information on cases and controls was obtained by self-administered questionnaire, which is generally considered less reliable than face-to-face interviews. The questionnaires were presumably completed by the subjects themselves in all cases, however, which is preferable to proxy-supplied information. The information supplied was not verified from other sources, as noted by the authors in reference to testing for biomarkers of exposure to tobacco smoke (they note that laboratory tests can only detect recent exposure, but they could still be useful in eliminating current smokers who may misreport themselves as never-smokers). Although cases and controls were newly diagnosed patients within a short time period in the eight participating hospitals and were supplied with the same questionnaire, there are still some questions regarding the comparability of cases and controls and their representativeness of the target population.

Controls tend to be younger than cases: Mean ages are 56 and 60, respectively, and 33% of controls, compared to 14% of cases, are below the age of 40. Controls also tend to be more educated than cases, with 69% of controls having completed 10 or more years of education compared to 52% of cases. Differences in age and educational level further reflect differences in lifestyle and socioeconomic status that may affect risk of disease. Also, the controls are

predominantly cancer patients too, almost half with breast cancer. Although the diseases of the controls may not be known to be related to tobacco use, controls may be a biased sample (as noted by the authors). Furthermore, the statistical analysis stratifies on age and education so, even though cases and controls were not strictly matched on these variables, the reported results should not be due to confounding by either of these factors. On the other hand, exclusion of breast cancer controls reportedly leaves the results unchanged.

Although some of the issues and reservations described above are methodological in nature and apply to the study throughout, others are specific to the ETS data alone. For example, one might expect a question regarding the use of cooking with wood or straw at age 15 and at age 30 to be open to little subjective interpretation or error in recall, presuming that methods of cooking persisted for several years between changes within a household. Although there is some suggestive evidence of increased lung cancer from ETS exposure (the reservations above set aside for the moment), the statistical evidence may be stronger for an association between lung cancer prevalence and use of wood or straw for cooking at age 30. Further support is provided by the observation that among those who had used wood or straw for cooking at age 30, 90% had also used those fuels at age 15, suggesting extended exposure in most cases. The age distribution of those exposed to wood or straw cooking is not given, but exposure at 30 years of age and before would allow for the long latency expected for lung cancer because 86% of the patients are at least 50 years of age.

The smoke from cooking sources may obscure or distort any impact of ETS exposure because the two sources probably contain some of the same carcinogens. The temporal dimension of exposure may also be a factor because indoor smoke from cooking may be less common at present than 30 years ago in comparison to ETS exposure. Further statistical analysis to adjust the effect of ETS exposure for the presence of smoke from cooking might aid interpretation of the results in this study, depending on the extent of confounding present.

A.29. STOC

A.29.1. Author's Abstract

(*Note:* This study has not been published. Only the abstract is available, which is given below.)

"Risk factors for lung cancer among women who had never smoked cigarettes were examined in an ongoing, population based, case-control study conducted in Florida. One hundred and twenty-four primary carcinomas of the lung, and 241 control women who had never smoked were included. Results suggest that childhood and adult exposures to environmental tobacco smoke may increase the risk of lung cancer among women who never smoked cigarettes. Having a

husband who smoked cigarettes resulted in a statistically significant increase in risk of lung cancer among women who had never smoked, with an odds ratio of 1.8 (95% C.I. 1.1-2.9). A 40% increase in risk was observed among women with less than 25 years of exposure to a spouse who smoked, when compared to women who reported their spouse had never smoked, with the risk increasing to 60% among women exposed 25 years or longer.

When exposure to tobacco smoke in childhood was considered, the data were less consistent. Having a parent who had smoked during the respondent's childhood did not increase the risk of lung cancer. However, among those respondents with high levels of exposure to parental smoking, an excess risk, although not statistically significant, was observed. Never smoking women who accumulated 25 or more exposure years experience a 70% increase in risk (OR = 1.7, 95% C.I. 0.8-3.6) of lung cancer compared to women who reported neither parent had smoked cigarettes."

A.30. SVEN

A.30.1. Author's Abstract

"In a population based-case control study the association between female lung cancer and some possible etiological agents was investigated: 210 incident cases in Stockholm County, Sweden, and 209 age-matched population controls were interviewed about their exposure experiences according to a structured questionnaire. A strong association between smoking habits and lung cancer risk was found for all histological subgroups. Relative cancer risk was found for all histologic subgroups. Relative risk for those who had smoked daily during at least one year ranged between 3.1 for adenocarcinoma to 33.7 for small cell carcinoma in a comparison with never-smokers. All histological types showed strong dose-response relationships for average daily cigarette consumption, duration of smoking, and cumulative smoking. There was no consistent effect of parental smoking on the lung cancer risk in smokers. Only 38 cases had never been regular smokers and the risk estimates for exposure to environmental tobacco smoke were inconclusive. The high relative risks of small cell and squamous cell carcinoma associated with smoking may have relative implications for risk assessments regarding passive smoking."

A.30.2. Study Description

This study was undertaken in Stockholm County, Sweden, from 1983 to 1986 to investigate the association between female lung cancer and some possible etiologic agents, particularly active and passive smoking. Because active smoking was an exposure of interest, cases and controls were not matched on smoking status; thus, the ETS study population is unmatched.

Cases are Swedish-speaking women with primary lung cancer from three Stockholm County hospitals who were willing and able to be interviewed between September 1983 and December 1985. Cases with carcinoid tumors were excluded from the ETS analysis. Both population and hospital-based control groups were assembled. Population controls were women randomly selected from the county population register, matched to a case on birthdate and interviewed between September 1983 and December 1986. Hospital controls were subjects originally interviewed as potential lung cancer cases but subsequently diagnosed with nonmalignant conditions. Population controls were enlisted and interviewed as soon as a case's diagnosis was confirmed, but because this confirmation took as long as a year after the interview, controls were not density sampled. Unblinded interviews were conducted face to face with all cases (and hospital controls) and 58% of the total population controls; the remainder were interviewed by telephone.

After exclusion of 21 potential cases due to initial diagnostic uncertainty, refusal, or illness precluding interview, 210 confirmed cases remained. Elimination of 172 ever-smokers and four subjects with carcinoid or not-microscopically-confirmed tumors left 34 never-smoking cases. Similarly, 209 population and 191 hospital controls were included in the total study, but a combined total of only 174 were never-smokers. The total case population averaged 62.5 years of age, but no other demographic information regarding cases or controls is provided. All cases used in the ETS analyses were histologically or cytologically confirmed primary lung cancers.

Daily smoking for at least 1 year is the criterion for a smoker; all other persons are considered never-smokers. Pipe and cigar smoking are never specifically addressed. Exposure to ETS is calculated for four sources: mother, father, home, and work. Having a smoking mother or father (at any time during ages 0-9 years) constitutes exposure to that particular source, whereas the presence of a smoker at home and work constitutes exposure. Adulthood and total lifetime exposure are considered separately for home and workplace exposure. Exposure levels are arbitrarily scored 1 for nonexposure, 2 for exposure to one source, and 3 for exposure to both sources in trend analyses of never-smokers, where exposures are considered in pairs (i.e., maternal and paternal smoking, home and workplace exposure). No other units of ETS exposure are used. Adenocarcinomas constituted 22, squamous cell 5, and small cell 2 of the 34 lung cancers occurring among never-smokers in the ETS population; no further histologic details regarding the ETS study population are provided.

To maximize available case numbers, parental smoking was first analyzed among all cases and community controls using stratification to adjust for active smoking (cig./day) and age. A risk of 1.8 (95% C.I. = 0.5-7.0) was estimated for maternal smoking and 0.8 (0.3-1.4) for paternal

smoking. A trend analysis in which maternal, paternal only, and no parental smoke exposure were scored as 3, 2, and 1, respectively, revealed no indication of trend ($p = 0.9$). Analyses restricted to never-smokers used both community *and* hospital-based controls combined. Among cases (controls), for childhood up through 9 years of age, 3 (5) had smoking mothers, 12 (71) had smoking fathers (but not mothers), and 19 (98) were unexposed. This yielded an age-adjusted risk estimate of 3.3 for maternal smoking (with or without paternal smoking) and 0.9 for paternal smoking during childhood. Adult exposure at home *and* at work yielded an estimated risk of 2.1, whereas exposure at home *or* work yielded a risk of 1.2. For lifetime exposure, the estimated risks for exposure as both a child *and* adult and as either a child *or* an adult were 1.9 and 1.4, respectively. None of these associations were statistically significant, and no significant trends were observed. The authors conclude that the results pertaining to ETS in the present study were not conclusive. The small number of never-smokers among the cases could be one important reason. It should be noted, however, that most of the point estimates of relative risk were greater than unity, which agree with results from previous studies on ETS exposure and with risk estimates concerning active smoking.

A.30.3. Comments

This study was undertaken to explore the role of active as well as passive smoking in lung cancer. After exclusion of active smokers, the available number of cases is too small to yield much statistical power.

Cases and population-based controls were initially matched on date of birth, but this matching was abandoned in the ETS analysis; furthermore, unmatched hospital-based controls are combined with the population-based controls in most analyses to boost available numbers. The comparability of these groups is thus unclear, and the authors provide no demographic comparisons to facilitate assessment of this potential problem. The reported similarity of results using only population-based controls is reassuring, but no details are provided as to *how* similar results actually were.

Diagnostic misclassification of cases is unlikely, given the histological or cytological confirmation of all cases and exclusion of secondary cancers. All cases were interviewed face to face, but 42% of controls were interviewed by telephone. The accuracy of responses may thus be lower for controls than for cases. And because interviews were not conducted blindly, inflation of estimated associations through interview bias is possible. A potential bias is also introduced by the rather large amount of active smoking required for classification as an ever-smoker. This allows considerable active smoking among persons in the never-smoker group, the effect of which could

mask an effect of passive exposure, or, if covarying positively with passive smoking, cause overestimation of association.

The first set of analyses of paternal and maternal smoking includes ever-smokers while attempting to adjust for active smoking on the basis of average daily cigarette consumption. The adequacy of this adjustment is questionable given the large estimated risks associated with active smoking relative to those posited for passive smoking, so the elevated estimated risks for maternal smoking obtained in these analyses are of questionable validity.

Restriction of the analyses to never-smokers similarly produces an elevated odds ratio for maternal smoking of 3.3, but the numbers involved (three cases and five controls) are so small that this value is quite unstable. A pattern of increasing estimated risk with increasing sources of exposure (at home or at work) as an adult and increasing periods of exposure (in childhood or adulthood) over the lifetime is suggestive of an association between lung cancer and ETS, but again small numbers preclude statistical significance of these results.

Restriction of the study population to females rules out the possibility of confounding due to gender. The likelihood of an ethnicity effect is reduced by restriction to Swedish-speaking residents of Stockholm County, and age is reportedly controlled for in all analyses. No other potential confounders are addressed. For example, marital status is not considered in the analyses of spousal smoking, leaving open the possibility that nonsmoking-related differences between married and unmarried women contributed to the observed association. The reported similarity of results when only population controls were used instead of hospital and population controls combined provides a general argument against confounding, although no specifics regarding the degree of similarity were supplied.

In summary, this study presents consistent evidence of associations between lung cancer and maternal, home, and workplace passive smoking exposure. Limited numbers preclude statistical significance and interviewer bias or confounding due to dietary or other factors cannot be ruled out as contributors to the observed results. Bearing these limitations in mind, the study's results are inconclusive but (excluding the analyses that include active smokers) do make a useful contribution to the pool of information available regarding ETS and lung cancer.

A.31. TRIC

A.31.1. Author's Abstract

"Fifty-one women with lung cancer and 163 other hospital patients were interviewed regarding the smoking habits of themselves and their husbands. Forty of the lung cancer cases and 149 of the other patients were nonsmokers. Among the nonsmoking women there was a

statistically significant difference between the cancer cases and the other patients with respect to their husbands' smoking habits. Estimates of the relative risk of lung cancer associated with having a husband who smokes were 2.4 for a smoker of less than one pack and 3.4 for women whose husbands smoked more than one pack of cigarettes per day. The limitations of the data are examined; it is evident that further investigation of this issue is warranted."

A.31.2. Study Description

This study was undertaken in Athens, Greece, to investigate the relationship of spousal smoking and lung cancer. All female Caucasian Athenian residents admitted to one of three chest or cancer hospitals in Athens and assigned a final diagnosis of lung cancer other than adenocarcinoma and alveolar carcinoma from September 1978 through June 1980 were interviewed by a physician. Controls were gathered from nonsmoking female Caucasian Athenian patients hospitalized during the same time period in the Athens Orthopedic Hospital. Some prevalent cases were thus presumably included, so control sampling probably approximated a density approach but did not strictly conform to one.

Diagnostic information was obtained from patients' charts. Exposure information was obtained by face-to-face unblinded interviews conducted by the same physician for all subjects. A total of 51 cases and 163 controls were interviewed. Of these, 11 cases and 14 controls reported themselves to be active smokers, leaving 40 cases and 149 controls as ETS subjects. No interview refusals are reported. Mean age of cases (controls) is 62.8 (62.3) years. Husband's education was marginally higher in controls than cases with 63% and 58% of spouses having completed primary school, respectively. No other demographic comparisons are reported for the ETS subjects alone. For the sample population including smokers, factors such as age, duration of marriage, occupation, education, and urban versus rural residence are all similar for cases and controls, except once again educational level is slightly higher for controls. There is no indication that verification of diagnosis or exclusion of secondary lung cancers was undertaken in cases. Of the 51 total cases, 14 were diagnosed histologically, 19 cytologically, and 18 by radiological or clinical means. No breakdown is given for the ETS subjects alone.

The study classifies as nonsmokers both reported never-smokers *and* former smokers who quit more than 20 years ago. It is not mentioned whether cigar and pipe smoking are considered as sources of exposure. Nonsmoking women are considered exposed to ETS if they are married to a man classified as a smoker. The average number of cigarettes smoked per day by the husband and the number of years of marriage are used to estimate the total number of cigarettes smoked by the husband during marriage. No data on childhood or nonspousal ETS exposure were collected.

Single women are grouped with women married to a nonsmoker and are thus considered unexposed. Widowed or divorced women were classified according to their former husband's smoking status on the assumption that smoking stopped at death or divorce. No checks of exposure information are reported.

For ETS subjects, the number of cases (controls) exposed over the total is 29 to 40 (78/149). The crude odds ratio calculated by the reviewers is 2.4 (95% C.I. = 1.12-5.16). The results presented in the article are all stratified by level of husband's smoking. The odds ratios are 1.8, 2.4, and 3.4 when the husband is a former smoker, smokes 1 to 20 cigarettes per day, and smokes 20 or more cigarettes per day, respectively. No confidence intervals are given, but a test for upward trend was statistically significant ($p < 0.02$). When ETS exposure is estimated by total number of cigarettes smoked during marriage, odds ratios (1.3, 2.5, and 3.0) increase with cumulative exposure (1-99, 100-299, and 300+ thousand, respectively). The upward trend remains statistically significant at $p < 0.02$. No analyses adjusted for age or other potentially confounding variables. With regard to age and other demographic variables, the authors conclude from the similarity of cases and controls that it is not necessary to stratify for these variables in the analysis, particularly because none is significantly associated with smoking in the study.

The authors note that this study has obvious limitations and is offered principally to suggest that further investigation of this issue should be pressed. Most seriously, the numbers of cases are small. Nevertheless, the association is in the direction expected if passive smoking is related to lung cancer, and the outcome is unlikely to be due to chance. Other limitations noted include the high percentage (35%) of cases lacking cytology and the selection of controls from a hospital different from those of the cases; it is argued, however, that neither of these appears to be consequential. The observation is made that it is potentially easier to detect an effect of passive smoking in the Greek population than in most Western populations, because in the latter groups, the overwhelming effects of active smoking, together with the high correlation between smoking habits of spouses, would tend to confound and conceal the lesser effects of passive smoking.

A.31.3. Addendum

In a letter to the editor of *Lancet* in 1983, Trichopoulos et al. released a data table derived from extension of subject collection through December 1982. This nearly doubled the sample size used in the 1981 publication, yielding 77 nonsmoking cases (102 total) and 225 smoking controls (251 total). The crude odds ratio calculated by the reviewers is 2.08 (95% C.I. = 1.20-3.59). The results for the expanded study show very little change; (estimated) relative risks when husbands

are former smokers, (1-20 cig./day and > 20 cig./day) compared to nonsmokers are 1.95, 1.95, and 2.54, respectively. The test for upward trend in the dose-response is significant ($p = 0.01$). No other analyses are presented.

A.31.4. Comments

This study was conceived and undertaken to explore the association of spousal smoking with lung cancer and does not rely on a preexisting data set. Thus, the investigators were in a position to design their selection and data collection to maximize the strength of their findings. This did not, however, prevent the appearance of some design and analytical flaws.

Demographics of the total case and control populations are very similar. All subjects in the spousal smoking analysis are resident Athenian nonsmoking women hospitalized in the same area of Athens; case and control groups have very similar mean ages, and their husbands are comparable in education. Thus, the groups probably have good demographic comparability, although it would have been helpful if the detailed demographic comparisons were focused on the nonsmokers alone. Most of the controls (108 out of 163) were being treated for fractures, a relatively minor and nonchronic illness compared to lung cancer, which may make them more representative of the general community than of hospitalized patients as a whole. This should reduce the problem of inclusion of smoking-related illnesses in the control group.

Although the researchers sought to exclude adenocarcinomas and alveolar carcinomas, presumably considering these would be less smoking-related, nearly two-thirds of the cases were not histologically confirmed, so an indeterminate number of these cell types was probably included. More important, the infrequency of histologic confirmation and lack of mechanisms to verify diagnoses or primary tumor status introduces potential for misclassification. The likely effect is a bias toward no association.

The researchers clearly devoted considerable thought to the smoking and exposure criteria, particularly with regard to changes in smoking and marital status over time. Single women were, however, automatically classified as unexposed. The authors contend that this is warranted by the traditional nature of Greek society and report that analyses restricted to married women result in similar, and still statistically significant, associations, although with somewhat lower estimated risks. There is a small reduction in the odds ratios after exclusion of single women, however, and the restriction of the full analyses and results to married women may have been useful.

Another issue related to exposure concerns inclusion of former smokers in the study, provided they had not smoked for at least 20 years. Active smoking 20 to 30 years before the onset of lung cancer may be of etiological relevance, however, in view of a long latency period for

lung cancer. Although use of the same interviewing physician for all subjects eliminates the problem of interobserver variability, it magnifies the potential problem of interviewer bias in exposure assessment, presumably toward a positive association, because the interviews were apparently conducted unblinded (virtually unavoidable with regard to diagnosis, given that controls were drawn from orthopedic trauma and rheumatology wards).

A larger concern, however, is the issue of potential confounders. It is contended that the similar distribution of demographic variables between cases and controls eliminates the need to consider these variables in the analyses, but similarity between cases and controls does not preclude confounding from an independent risk factor differentially distributed by *exposure*. More convincing is the contention that these variables were not significantly associated with smoking in these data, although no specifics are included. Potential confounders such as diet, cooking, and heating practices are not addressed. The appearance of a statistically significant trend, for ETS exposure measured by either current spousal smoking or cumulative cigarette consumption during marriage, supports an association between spousal smoking and increased lung cancer incidence.

Overall, the issues addressed above would probably produce a conservative bias, resulting in an underestimate of the degree of association. The study's basic design is sound. It provides statistically significant evidence of dose-response, and although the limitations described above should be borne in mind, it provides useful data for assessment of the relationship between ETS and lung cancer.

A.32. WU

A.32.1. Author's Abstract

"A case-control study among white women in Los Angeles County was conducted to investigate the role of smoking and other factors in the etiology of lung cancer in women. A total of 149 patients with adenocarcinoma (ADC) and 71 patients with squamous cell carcinoma (SCC) of the lung and their age- and sex-matched controls were interviewed. Personal cigarette smoking accounted for almost all of SCC and about half of ADC in this study population. Among nonsmokers, slightly elevated relative risk(s) (RR) for ADC were observed for passive smoke exposure from spouse(s) [RR = 1.2; 95% confidence interval (CI) = 0.5, 3.3] and at work (RR = 1.3; 95% CI = 0.5, 3.3). Childhood pneumonia (RR = 2.7; 95% CI = 1.1, 6.7) and childhood exposure to coal burning (RR = 2.3; 95% CI = 1.0, 5.5) were additional risk factors for ADC. For both ADC and SCC, increased risks were associated with decreased intake of β-carotene foods but not for total preformed vitamin A foods and vitamin supplements."

A.32.2. **Study Description**

This study was undertaken in California during 1981 and 1982 to investigate the role of smoking and other factors in the etiology of lung cancer in women. These other factors included prior lung disease, coal heating and cooking, diet, and occupation. Both active and passive smokers are included; some of the ETS analyses retain active smokers while attempting to adjust for smoking status.

Cases are white female English-speaking Los Angeles County residents under 76 years of age at time of diagnosis with primary adenocarcinoma or squamous cell cancer of the lung between April 1, 1981, and August 31, 1982. Cases are restricted to U.S.-, Canadian-, or European-born individuals with no history of prior cancer other than nonmelanoma skin cancer. Controls are density sampled, matched individually on neighborhood and age (± 5 years), and meet all case criteria (except, of course, diagnosis of lung cancer). The L.A. County tumor registry was used to identify incident cases for inclusion in the study, whereas controls were recruited house to house. Interviews to obtain exposure data were conducted by telephone with participating subjects, apparently unblinded.

A total of 490 eligible cases were identified; 270 were not interviewed because they were too ill or had died (190), their physician refused permission to contact them (28), they could not be located (8), or they refused (44). Those not interviewed did not differ significantly from those interviewed with regard to age or their marital, religious, or smoking status as recorded on registry records. Refusals eliminated 70 potential controls. The case and control populations had nearly identical mean ages for adenocarcinoma, 59.7 versus 59.5 years, respectively, and for squamous cell cancer, 61.4 versus 61.1 years. No other demographics are provided. Histologic diagnoses were obtained for all cases.

For spousal smoking, exposure constitutes having a spouse who smoked while living with the subject. For workplace smoke, exposure is based on the opinion of the subject. It is not clear whether for the lung cancer analyses, parental smoking refers only to adult life (as for spousal and workplace exposure) or to the childhood and teen years (as was stipulated for coal and preadult lung disease exposures). Adult life seems most probable. Units of exposure for spousal and parental smoking are cigarettes per day and years of exposure, apparently entered into a regression model as a combined variable; for occupational exposure, units are in years of exposure. Exposure data were apparently not checked, treatment of cigar and pipe smoking is never mentioned, and no results are reported for household smoking aside from spouse and parents, although information on this exposure was collected. Never-married women were excluded from the spousal smoking analysis, but marital status was not otherwise considered in the analyses. The

only histologic or airway proximity information provided for the ETS subjects is that 29 adenocarcinomas occurred among nonsmokers, 12 of which were bronchoalveolar.

The total study population includes 220 cases and an equal number of matched controls. Of the cases, 149 are adenocarcinoma and 71 are squamous cell. Nonsmokers constituted 29 of the adenocarcinoma cases and 62 of the corresponding controls, while composing 2 of the squamous cell cases and 30 of the controls. No raw data are presented regarding passive smoking and lung cancer. Logistic regression analysis of matched pairs was used in all calculations. Results restricted to nonsmokers are presented only for adenocarcinoma. An estimated relative risk of 1.2 is found for spousal smoking, 1.3 for workplace exposure, and 0.6 for smoking by either parent. None of these estimates was statistically significant. Exposure from spouses and at work, however, show a dose-response trend with years of exposure, yielding estimated relative risks of 1., 1.2, and 2.0, for 0, 1 to 30, and 30 or more years of exposure, respectively.

Analyses that include active smokers but attempt to adjust for them by including the number of cigarettes smoked per day and age at start of smoking in a logistic regression model are presented for both lung cancer types. For adenocarcinoma, estimated relative risks for maternal, paternal, spousal, and workplace exposure of 1.7, 1.3, 1.2, and 1.2, respectively, were obtained. For squamous cell cancer, maternal, paternal, spousal, and workplace relative risks are 0.2, 0.9, 1.0, and 2.3, respectively. None of these estimates is statistically significant.

History of lung disease at least 5 years prior to diagnosis of lung cancer reportedly had no significant association with lung cancer. History of lung diseases before age 16 yielded a significant association for pneumonia (RR = 2.7 [95% C.I. = 1.1-6.7] for adenocarcinoma and RR = 2.9 [95% C.I. = 0.5-17.4] for squamous cell cancer) but not for six other diseases.

Heating or cooking with coal during the childhood and teenage years is also significantly associated with lung cancer (RR = 2.3 [95% C.I. = 1.0-5.5)] for adenocarcinoma and RR = 1.9 [95% C.I. = 0.5, 6.5] for squamous cell). Among dietary factors, low beta carotene consumption is significantly associated with adenocarcinoma (RR = 2.7) and mildly associated with squamous cell (RR = 1.5). Diets low in dairy products and eggs have similar relative risk values. No significant associations were noted for vitamin A consumption, occupation, or other health history factors not previously considered.

The authors conclude that the etiology of squamous cell carcinoma can be explained almost entirely by cigarette smoking. Cigarette smoking, however, explains only about half of the adenocarcinoma cases. On the basis of this study, childhood lung disease and exposure to coal fires in childhood explain at least another 22% of adenocarcinoma cases. Passive smoking and

vitamin A may be involved, but more research is needed to clarify their roles in lung cancer etiology.

A.32.3. Comments

This study took particular care with its treatment of case and control assembly. Extensive inclusion criteria extending to both groups, matching not only on age but neighborhood of residence, and retention of matching through analysis all bode well for comparability of cases and controls. The virtually identical mean ages of cases and controls indicate the success of these efforts. In addition, exclusive use of incident cases reduces the potential for selection bias, and density sampling of controls reduces potential problems with temporal variation. The only real fault in the treatment of cases and controls is the failure to provide any demographic comparison other than for age, thus denying concrete confirmation of high case-control comparability.

Case diagnoses are likely to be accurate, because all were histologically diagnosed, making misclassification unlikely and making cell-type-specific analyses possible. Although no one pathologist or team verified these determinations, the authors note that there is generally good interobserver agreement for the cell types included in this study. Potentially eligible cases not interviewed due to illness, refusal, or other reasons did not differ significantly in demographic or smoking status from those actually interviewed, again arguing against biased selection.

No proxy interviews were used and all subjects were English-speakers, enhancing the chances of obtaining accurate exposure information. On the other hand, interviews were by telephone—possibly decreasing accuracy relative to face-to-face interviewing--and apparently unblinded, thus introducing possible interviewer bias toward positive results.

Collection of exposure data seems generally adequate, except that treatment of pipe and cigar smokers is not described. Uncertainty on this point extends to the analysis and is coupled with a vague treatment of parental smoking (current only? childhood only? or both?) and lack of treatment of household smokers other than parents or spouses, despite collection of data on this point. These uncertainties probably translate into nondifferential exposure misclassification, biasing results toward the null.

The analyses themselves suffer from the common problem of restricted numbers of nonsmoking cases—29 for adenocarcinoma and only 2 for squamous cell. Some factors examined are restricted to nonsmokers alone for adenocarcinoma, but for most analyses, an adjustment for active smoking by logistic regression modeling was attempted. The adequacy of such adjustment may be questionable. For adenocarcinoma, however, the results for passive smoking were very similar, regardless of whether restriction or adjustment was used. Further, a dose-response

pattern was seen for cumulative years of spousal and workplace exposure among nonsmokers. The utility of the smoking-adjusted cell analyses is nevertheless questionable, given the paucity of nonsmoking cases.

The findings of substantial associations between lung cancer (or, at least, adenocarcinoma) and childhood pneumonia and coal burning are of interest. It must be borne in mind that seven adult respiratory diseases (including pneumonia) as well as six other childhood respiratory diseases were examined, so the possibility that the pneumonia association was an artifact of multiple comparisons cannot be ruled out. History of hysterectomy and multiparity showed nearly significant associations with adenocarcinoma, but it is not clear how many other health history factors were also considered. Coal burning has been associated with lung cancer in several other studies. Similarly, as in several other studies, one found an association with low beta carotene intake, but there was no evidence of a dose-response gradient, and no significant association was found for preformed vitamin A. The strongest association with a dietary factor was actually that for low intake of dairy products and eggs, which showed a consistent dose-response pattern. The use of a matched-pair analytical approach controls for possible confounding due to age or neighborhood, which also reduces the likelihood of neighborhood-related factors such as socioeconomic status as major sources of bias. Confounding due to active smoking can be ruled out in the passive smoking results for adenocarcinoma and is not likely in regard to other factors given adjustment for this variable in all analyses. Likewise, the authors report that adjustment for childhood pneumonia, coal burning, and beta carotene intake did not alter their results. Strangely, however, no adjustment for dairy product and egg intake--the dietary factor with the most convincing association with lung cancer in their data--was carried out.

Overall, this study's results are consistent with a mild association between spousal and workplace ETS exposures and lung adenocarcinoma, although they support no such association for parental smoking. In addition, the study it raises childhood pneumonia, coal burning during early life, low intakes of beta carotene, and low intake of dairy products and eggs as potential moderate risk factors that should be considered by future studies. The results for squamous cell carcinoma are uncertain given the small number of nonsmoking cases available, and in all instances, they lack statistical significance due to sample size limitations. Thus, the study provides useful information on the relationship of adenocarcinoma of the lung with ETS and a number of other factors: information regarding squamous cell cancer is of much lower utility.

A.33. WUWI

A.33.1. Author's Abstract

"A case-control study of lung cancer involving interviews with 965 female patients and 959 controls in Shenyang and Harbin, two industrial cities which have among the highest rates of lung cancer in China, revealed that cigarette smoking is the main causal factor and accounted for about 35% of the tumors among women. Although the amount smoked was low (the cases averaged eight cigarettes per day), the percentage of smokers among women over age 50 in these cities was nearly double the national average. Air pollution from coal burning stoves was implicated, as risks of lung cancer increased in proportion to years of exposure to Kang and other heating devices indigenous to the region. In addition, the number of meals cooked by deep frying and the frequency of smokiness during cooking were associated with risk of lung cancer. More cases than controls reported workplace exposures to coal dust and to smoke from burning fuel. Elevated risks were observed for smelter workers and decreased risks for textile workers. Prior chronic bronchitis/emphysema, pneumonia, and recent tuberculosis contributed significantly to lung cancer risk, as did a history of tuberculosis and lung cancer in family members. Higher intake of carotene-rich vegetables was not protective against lung cancer in this population. The findings were qualitatively similar across the major cell types of lung cancer, except that the associations with smoking and previous lung diseases were stronger for squamous/oat cell cancers than for adenocarcinoma of the lung."

A.33.2. Study Description

The objective of this study was to evaluate the role of potential risk factors for lung cancer in Harbin and Shenyang, two cities among those with the highest mortality rate for lung cancer in China. Active smokers are included in the cases, so data on ETS subjects constitute a subset of the whole study.

Cases consist of female residents under age 70 newly diagnosed with primary lung cancer in about 70 participating hospitals in Harbin and Shenyang between 1985 and 1987. Controls are female residents randomly selected from the general population of these cities and frequency matched by 5-year age group to the age distribution of female lung cancer cases reported in the cities in 1983. Trained interviewers collected information on smoking habits, diet, cooking and heating practices, and other factors from subjects in face-to-face unblinded interviews.

A total of 1,049 qualifying cases were found, including both ever-smokers and never-smokers, of which 405 were diagnosed by histology, 309 by cytology, and 351 by radiology or clinical means. (Note: These diagnostic numbers do not total 1,049. The 351 figure may be

intended to be 251, which would give a total of 965 diagnoses, about the number of cases interviewed.) Of these, 85 either died prior to interview, refused to participate, or could not be located. Mean age of participating cases was 55.9 years, whereas that of the 959 controls was 55.4 years. Nonsmokers compose 417 of the interviewed cases and 602 of the controls.

A smoker is defined as a person who has smoked cigarettes for 6 months or longer, so a nonsmoker apparently may have smoked up to 6 months. Information on all types of tobacco products smoked was collected. Sources of ETS exposure include smoking by any household cohabitant and smoking by individuals (spouse, mother, and father) over the course of the subject's lifetime. Exposure at the workplace is also addressed. ETS exposure in the home is expressed in terms of cigarettes per day and number of years smoked; no units of measurement are used for workplace smoking. No checks on exposure data were undertaken. Marital status of subjects is not discussed. Of the cases with histological or cytological data, adenocarcinomas compose 310 (41.7%), squamous cell cancers 201 (28.9%), small and oat cell cancers 117 (16.8%), and large cell or unspecified types 66 (9.5%). No data on airway proximity or diagnostic breakdowns limited to nonsmokers are provided.

Statistical analyses of potential risk factors, including ETS, largely include data on active smokers and then adjust for the effect due to smoking by logistic regression, along with other potential confounders such as age, education, and location. These analyses indicate no increase in risk from household sources of ETS, with estimated relative risks of 0.8 (household cohabitants), 0.9 (spouse), 1.0 (mother), and 1.0 (father). The estimated risk for workplace exposure is nonsignificant (RR = 1.2). Restriction of analyses to ETS subjects alone (i.e., only the nonsmokers) produced similar results, with estimated relative risks of 0.7 for general cohabitant, 0.7 for spouse, 0.9 for mother, 1.1 for father, and 1.1 for workplace exposure. The ETS exposure from spousal smoking is significantly low (i.e., associated with a *decrease* in lung cancer by this analysis, as apparent from the confidence interval; RR = 0.7; 95% C.I. = 0.6-0.9).

The smoking-adjusted analyses indicate associations with lung cancer for several types of heating devices, including kangs (brick beds heated by pipes from the stove or by burners directly underneath), coal stoves, and heated brick walls or floors. The risk associated with the use of burning kangs (those heated by stoves underneath) shows an upward trend with years of use, becoming statistically significant at 21 or more years of use (RR = 1.5; 95% C.I. = 1.1-2.0). Significantly elevated risks are also associated with use of heated brick walls or floors (RR = 1.5 [1.1-2.1] for 1-20 years of use; RR = 1.4 [1.1-1.9] for > 20 years). Nonsignificant increases in risk are noted for use of kangs of all types, coal stoves, and coal burners; nonsignificant reductions in risk are indicated for noncoal stoves and central heat. Use of deep frying at least twice a month

and eye irritation during cooking are both significantly associated with lung cancer, as are regular intake of animal protein and fresh fruit. (Note: Multiple comparisons may be a factor for the apparent significance of some items, as discussed further in the next section.)

The authors find no overall association between lung cancer and ETS exposure. On the other hand, coal burning, exposure to cooking oil fumes, and chronic lung disease may all be risk factors. Consumption of beta carotene shows no evidence of a protective effect. Overall, active smoking is the major cause of lung cancer among women in the regions sampled.

A.33.3. Comments

The sample size is impressive, with ETS exposure data available for nearly 1,000 cases including smokers and over 400 cases when restricted to nonsmokers, thus providing substantial statistical power. All subjects are women recruited from two industrial cities in northeast China, reducing potential for complications due to regional or urban-rural differences. Nearly all of the hospitals in these cities were involved, all cases occurring in these hospitals were targeted, and the rate of participation among eligible cases was high; thus potential for selection bias is minimized. The effective case recruitment in combination with the use of general population controls maximizes generalizability of the study's results for northeast China. It would have been useful, however, to present the results for the two component study locations separately. Although coordinated in planning and execution, there are two separate study locations and the sources of heterogeneity between them tends to be obscured when results are combined.

Unfortunately, the study's results with regard to ETS are more limited than the strengths listed above might suggest. The inclusion of age, education, and location as control variables in all analyses is laudable, thus eliminating three sources of potential confounding. The attempt to control for potential sources of confounding that may be causally related to lung cancer by statistical methods, however, is less certain. Although some analysis was conducted with data for active smokers included, to the authors' credit they also analyzed data for ETS subjects alone (i.e., with the data for active smokers removed), which is the surest way to control for confounding by active smoking. Other potential causes of lung cancer (e.g., air pollution from coal-burning stoves, smokiness during cooking, and deep-fat frying foods) also need to be taken into account in an analysis of ETS. This cannot always be accomplished effectively by statistical methods, particularly when there are multiple risk factors to be taken into account that are variable, poorly measured, and possibly more potent risk factors than ETS may be.

At the risk of belaboring this point, as the reader is aware, a case-control study is ideally designed and executed under conditions where cases and controls are as comparable as possible

aside from the factor of interest, such as ETS exposure. The presence of other risk factors may tend to pollute and obscure, much like the contamination of a laboratory experiment. In this same sense, the presence of indoor sources of smoke other than ETS may contaminate an environment for measuring ETS effects because the non-ETS smoke likely contains many of the same carcinogens as ETS, and possibly in much larger quantities, depending on the relative levels of exposure. Other factors outside the home, such as workplace exposure to coal dust and to smoke from burning fuel that was reported more often in cases than controls, contribute to the potential confounding in a similar way. Consequently, a credible analysis of ETS requires being able to adjust for these likely confounding factors satisfactorily, and the ability to do that depends on reliable measures of exposure and the extent of confounding. That kind of statistical analysis is not given in the article, and it does not appear to have been possible, based on conversations with the authors (Wu-Williams and Blot) and the text of the article: "Despite the large size of our study, we were unable to clarify the magnitude of risks due to passive smoking, recognized as a cause of lung cancer around the world (U.S. DHHS, 1986). Perhaps in this study population the effects of environmental tobacco smoke was obscured by the rather heavy exposures to pollutants from coal-burning Kang, other indoor heating sources, and high levels of neighborhood air pollution (Xu et al., 1989)."

The multivariate analysis reported in the article reinforces the viewpoint that any ETS effect may be dominated by the presence of other risk factors. In that analysis, variables were allowed to enter a logistic regression model in the order of their explanatory value (a stepwise regression exercise in statistical terminology). The order of entry into the model is deep frying, eye irritation, pneumonia, household tuberculosis, burning kang, self-reported occupational exposure to burning fuel, passive smoking, and heated brick wall or floor. Passive smoking, in this exercise, is significant ($p < 0.05$) but in the direction of reducing lung cancer, not contributing to it. The 0.05 value, however is not fully meaningful as a significance level for ETS, because of the stepwise procedure used (the same data used in the construction of a model is used for testing variables in the model) and because of the likely confounding between ETS and other variables. Note, for example, that passive smoking entered the model ahead of heated brick wall or floor, which is highly significant when analyzed alone, whereas passive smoking is not.

The evidence for association of lung cancer with burning coal and deep frying foods is particularly provocative, as it indicates two factors that may play a substantial role in the etiology of lung cancer in northeast China and, hence, in other areas as well where such practices occur. The associations noted with other factors are also of interest, but their importance is undermined by the problem of multiple comparisons. In the table presenting results for dietary factors, for

example, 26 risk estimates are computed, 4 of which are significant at the 5% significance level (for a two-sided test, 2.5% level for the test of an effect), only one more significant finding than expected due to chance alone.

Being somewhat speculative, the use of cases age 70 and below may be a factor. Wells (1988) showed that about half of the female passive smoking deaths occur after age 70, for the studies included in that reference. If ETS is a risk for lung cancer and if individual susceptibility to lung cancer is a factor, some of the stronger risk factors such as coal burning and cooking oil may have caused lung cancer in the more susceptible subjects before passive smoking had a chance to exert itself.

In summary, this large and basically well-executed study observed no significant association between exposure to ETS from cohabitants, spouse, parents, or workplace and lung cancer. Lack of control for a number of other significant risk factors identified in the study undermines these results, however. The associations with coal burning for heat and oil frying are particularly notable. Use of the heating devices most strongly linked with lung cancer is presumably more common in colder northern regions, whereas stir frying may be more widespread in Asian communities, without regard to climate. Thus, this study was exploratory, designed to generate hypotheses rather than to test the specific hypothesis that ETS exposure is associated with lung cancer. It identifies a number of potential risk factors for consideration in future studies. The prevalence of these factors in the study population combined with the lack of analysis of their association with ETS exposure, however, renders the results for ETS inconclusive.

APPENDIX B. METHOD FOR CORRECTING RELATIVE RISK FOR SMOKER MISCLASSIFICATION

B.1. INTRODUCTION

The purpose of this Appendix is to present the details of the method used in Section 5.2.2. to correct observed passive smoking relative risks for the systematic upward bias caused by misclassification of some smokers as never smokers. The method used is that proposed by A. J. Wells and W. F. Stewart (Wells, 1990). This Appendix covers: Section B.2) the principles of the method; Section B.3) how the method differs from those previously used by the National Research Council and P. N. Lee; Section B.4) the data used to calculate the misclassification factors and other parameters; Section B.5) the mathematical model used to calculate the corrected relative risks; and Section B.6) a numerical example to show how the method is applied in a practical case. Evidence is also presented indicating that the true downward corrections for smoker misclassification bias may be even smaller than those used in Section 5.2.2.

There is considerable literature on this topic and a history of controversy regarding the magnitude of the bias and whether it may explain the observed increase in lung cancer mortality due to ETS exposure. The NRC report on the health effects of passive smoking (NRC, 1986) delves into this topic in considerable detail. It concludes that bias is likely and estimates an adjustment for the summary relative risk from the combined results for all ETS studies. The NRC report further concludes that smoker misclassification does not account for the observed passive smoking risk. On the other hand, Lee in various publications (Lee, 1987b, 1988, 1990, 1991) has claimed that the smoker misclassification bias is large enough to explain most or all of the observed passive smoking lung cancer risk.

Approaches to estimation of misclassification bias have used mathematical modeling with parameters estimated from a variety of sources that have not always been consistent. The procedure described below attempts to rectify some previous sources of misunderstanding on this topic and utilizes the extensive data sources now available to improve parameter estimates and tailor refinements to individual populations.

B.2. PRINCIPLES OF THE WELLS-STEWART METHOD

The Wells-Stewart method is based on the following principles, the nature and need for which have largely become apparent from the chronological evolution and disparate approaches and results on this problem.

Parameters:

a. Limit the misclassifieds to those who said they never smoked, not simply to nonusers, because the latter would include self-reported former smokers, who are not a factor in the epidemiology.

b. Use one minus sensitivity or its close relative, false negatives (misclassified smokers) divided by observed positives (self-reported smokers) as the vehicle for transferring misclassification data from cotinine and discordant answer studies to the passive smoking studies. Sensitivity is the term used to describe the fraction correctly classified as exposed, namely true positives divided by true positives plus false negatives, but since we are assuming that the true positives and the observed positives are the same (no misclassification of never-smokers as smokers). Sensitivity in this case becomes observed positives divided by observed positives plus false negatives. Thence one minus sensitivity becomes false negatives divided by observed positives plus false negatives. Ignoring the false negatives in the denominator introduces negligible error. In any case do not use specificity (true negatives divided by true negatives plus false positives) or any parameter that uses as its denominator true or observed negatives (self-reported never-smokers). The reason is that sensitivity is affected much less by smoker prevalence than parameters based on observed negatives.

c. Calculate a correction for each epidemiologic study separately using a misclassified smoker relative risk and a proportion of smokers among subjects and spouses that is characteristic of the timeframe and locale of each study. Use data from the study itself or from another study with the same target population, if possible.

d. Use only female data to correct misclassification of female subjects.

Mathematical model:

Calculate the corrected risk directly--that is, do not first calculate a bias assuming no passive risk and then divide the observed risk by that bias to get a corrected risk.

Subjects found to be misclassified as nonsmokers are categorized according to their true smoking status--former or current. Current smokers are further classified as "regular" or "occasional", according to cotinine levels observed. "Regular" means the cotinine level is above 30% of the self-reported smoker mean; "occasional" applies to the range 10-30%. Cotinine levels are not informative for misclassified former smokers, who tend to be long term abstainers (10+ years, according to Lee (1987b) and Wald et al. (1986)). The two studies with detailed cotinine levels on female current smokers (Lee, 1986 and Haddow et al., 1986, in Table B-1) indicate that about 10% of the current smokers are occasionals.

B.3. DIFFERENCES FROM EARLIER WORK

The Wells-Stewart method differs from the method used by the NRC (1986), which is also described by Wald et al. (1986), in that the NRC method failed to separate the misclassified smokers into regular, occasional, and exsmokers, and they failed to account for the effect of smoker misclassification on active smoker risk. The NRC made an overall correction to the aggregated passive relative risk using United Kingdom smoking prevalence and risk rather than making the corrections study by study with appropriate smoking prevalences and risk for each study's time and locale, and they mixed male data with female data in arriving at misclassification factors. Their calculated bias of 1.34/1.25 = 1.07, or 7%, for the combined worldwide studies is substantially higher than the 2% overall bias that would result if the biases in Table 5-7 were aggregated. The discrepancy is largely due to NRC's use of U.K. parameters for all of the studies regardless of locale, plus some overestimation of the impact of misclassified occasional and exsmokers.

Lee's methods have evolved over the years in three stages. In Lee (1987b, 1988) he improved on the NRC method in that he divided the misclassified smokers into exsmokers and current, regular and occasional smokers, and he corrected the smoker risk for misclassification. However, all of the five principles listed above were violated to some degree resulting in about a twelve-fold overestimation of the bias. The Lee (1990) paper correctly limits misclassifieds to never smokers, relates misclassified smokers to smokers, not to never smokers, and treats each study separately, but still mixes male input data with female data for use in calculating bias for females. Furthermore, his (Lee, 1990) mathematical model still relies on the assumption of no passive risk, which results in increased estimates of the bias as the observed relative risk increases. In addition, Lee (1990) has changed from separating the misclassified smokers into three groups in favor of the (less useful)

overall category of ever smokers. Most recently Lee (1991) presents a more complex mathematical model that includes a term for passive risk, but the method still has the other shortcomings noted for Lee (1990). A comparison of the most recent Lee bias estimates with those in Table 5-7 is shown in Table B-2 for the five U.S. studies with the greatest statistical weight. When Lee's inputs are used with the Wells-Stewart mathematical model, the calculated biases are if anything somewhat larger than when using Lee's most recent model. Therefore, the difference between Lee's most recent estimates of bias and those shown in Table 5-7 are in practical terms due almost entirely to differences in input parameters. The input parameters we have chosen are developed in the next section, and comparison with the Lee parameter estimates are shown as footnotes to Table B-2.

B.4. PARAMETER ESTIMATES

The key input into these calculations is the proportion of misclassified regular current smokers who claim they have never smoked. Our definition of misclassified regular current smokers, first suggested by Lee (1987b), produces a mean cotinine level approximately equal to that of all self-reported current smokers. Detailed data from three large cotinine studies have been assembled for use herein with the cooperation of their principal investigators (Coultas, Cumming, and Pierce in Table B-3). The data identify individual nonsmokers with cotinine values greater than 10% of the mean for self-reported smokers, by sex and self-reported smoking status (never or former). Data on nonusers are also available from several other studies (the lower portion of Table B-3). Since the numbers of misclassified smokers are small, the proportions of misclassified smokers who would have said "never" versus "former" are estimated using the proportions observed in the first three studies. Data sets not differentiating outcomes by sex have not been used. Also the large 1986 study by Haddow and colleagues has not been used for this purpose on the advice of one of the authors (private communication from G.J. Knight).

The number of self-reported never- and former smokers with sufficiently high cotinine levels to be reclassified as current smokers is shown by study in Table B-3. As described above, those with cotinine levels in the 10-30% range are considered to be occasional smokers while those above 30% are treated as regular smokers. If it is assumed that 90% of 1,525 self-reported current smokers, or 1,372, are regular smokers, leaving 10%, or 153, as occasionals, then the percentage of current regular smokers misclassified as never-smokers totalled over all studies in Table B-3 is 14/1,372 or 1.02%. The percentage is almost the same if the number of true, i.e., self-reported plus misclassified current

regular, smokers is used. For the occasional smokers only, the misclassification rate is much higher, about 20% (15%) of observed (true) occasional smokers. It is possible, however, that the subjects classified as occasional smokers based on cotinine levels in the range 10-30% may contain some true never-smokers that are just highly exposed to passive smoke.

The studies in Table B-4 provide data on discordant answers, i.e., reported never-smokers who have called themselves smokers on one or more previous occasions. Based on those data, the estimated percentage of former smokers misclassified as never-smokers is about 12% (11%) of the observed (true) number of former smokers. As mentioned previously, evidence suggests (Wald et al., 1986; Lee 1987b) that most former smokers misclassified as never-smokers have been nonsmokers for an extended period, such as 10+ years, and may have been light smokers on average. Accordingly, we have used a weighted average of the data of Alderson et al. (1985), Lubin et al. (1984), and Garfinkel and Stellman (1988) for 10+ year abstainers to estimate former smoker relative risk, namely, an excess risk that is 9% of current smoker excess risk.

Some confusion and misleading conclusions on smoker misclassification have resulted from the practice of expressing the number of smokers misclassified as never-smokers as a percentage of the total number of (either true or observed) never-smokers, rather than as a percentage of the number of smokers. That leads to a higher expected percentage of smokers misclassified as never- smokers among cases than controls because lung cancer cases are much more likely to have been smokers than never-smokers. Some people have interpreted a higher percentage of observed never-smokers later found to be misclassified smokers among the cases as evidence that smokers with lung cancer are more apt to claim falsely to be never-smokers than persons without cancer. That conclusion, however, appears to be an artefact of treating the misclassification rate as a percentage of the number of never-smokers rather than as a percentage of the number of smokers. The study data summarized in Table B-5 do not support that conclusion. If anything, it is more supportive of the conclusion that ever-smokers in lung cancer studies may be less likely to misrepresent themselves as never-smokers than members of the general public who are questioned in community surveys. The one percent average misclassification rate shown in Table B-5 for the lung cancer cases suggests that estimates such as the 5.7% from the general population studies (Table B-5) or the near four percent of ever-smokers (Table B-4) that we have used may be much too high.

Further corroboration that the misclassification rates from the community studies are too high relative to those in the epidemiologic studies is found in the recent study by Fontham et al. (1991).

After eliminating possible smokers among the self-reported never-smokers by the usual epidemiologic techniques, the investigators found by cotinine measurements that only two probable occasional smokers and no probable regular smokers were left among the 239 never-smoking lung cancer cases for which cotinine measurements were made. Assuming 45% ever-smoking among controls and an ever-smoker relative risk of 8 for regular smokers and 2.4 for occasionals, there would have been 1,456 smoker cases, consisting of 1,409 current smokers and 47 occasional smokers. It is seen that a misclassification rate of 0/1,409 = 0.00% for regular smokers is well below the 1.0% that we have used from the community surveys, and 2/47 = 4.3% for occasionals is also well below the 19.6% for occasionals that we have used.

Another indication that the estimates based on community surveys may be too high comes from analysis of male data. The observed percentage of never-smokers is typically much lower for males (17% to 35%) than females (41% to 86%). To correct for smoker misclassification we set up a deletions table analogous to Table B-15 where the number of current and former smokers misclassified as never-smokers are subtracted from the reported number of never-smokers. When the misclassification rates generated from community surveys are applied to the male data, the outcome is not credible--the number deleted for misclassification exceeds the total number of reported never-smokers in three of the eleven examples of which we are aware and drives the corrected relative risk well below unity in four more. This outcome indicates that the misclassification rates derived from the community surveys are too high. It is probable that the true smoker misclassification bias is on the order of one-fourth to one-half of the values shown in Table 5-7.

It is also said that East Asian women misclassify themselves at much higher rates than Western women. The data from the International Agency for Research on Cancer in Table B-3 do not support that claim, however, because the East Asia (Hong Kong, Japan, and China) misclassification rate for current regular smokers is 1/77 = 1.3%, not much different from the overall rate of 1.0%.

The main proponent of the idea that smoker misclassification accounts for most or all of the observed passive smoking risk has been P.N. Lee (1986, 1987b, 1988). He has estimated the bias for females to be as high as 1.24. However, his methods are open to considerable question. He used "nonuser" cotinine data, which includes people who said or would have said they were former smokers, rather than using only data on people who said they never smoked. This would about double the calculated bias. He averaged high male misclassification rates into low female misclassification rates. He made an overall correction to the combined risk using modern U.K. smoker risk and

smoking prevalence rather than making the corrections study by study, as is done here with smoker risks and prevalence appropriate for each study. He transferred misclassification rates from the cotinine and discordant answer studies using percent of never-smokers rather than percent of smokers. He also used as an input the data from the large Haddow study (Haddow et al., 1987) when the authors state (private communication from Dr. George Knight) that the data from the study should not be used for misclassification studies. Also Lee's mathematical method tends to overstate the bias for passive risks greater than about 1.3. At a risk of two, his method overstates the bias about 100%.

In conclusion, it would appear that the bias introduced by misclassification of smokers as never-smokers is not a serious problem. It probably increases perceived relative risks on a worldwide basis by 1% to 2%, with the effect being about three times as large for combined U.S. studies.

B.5. MATHEMATICAL MODEL

The proportion of observed smokers, m_{h0}, misclassified as never-smokers is estimated separately for former smokers (m_{10}), occasional smokers (m_{20}), and regular smokers (m_{30}). Similarly, the proportion of observed current smokers, m_{h1}, misclassified as former smokers is estimated separately for occasional smokers (m_{21}) and regular smokers (m_{31}). These estimates are given in Tables B-3 and B-4. It is assumed that there is no misclassification of true never-smokers as current or former smokers or of observed former smokers as current smokers. Also these misclassification factors are used for all the studies unless otherwise noted. We suspect that misclassification rates probably vary from study to study. That variability, however, would tend to cancel out as the individual study results are combined.

Let c_{ijk} designate the observed proportionate distribution of controls (i = 0) and cases (i = 1) by their smoking status (j = 0,1,2,3) and the smoking status of their husbands (k = 0,1) as illustrated in Table B-6. Following the notational convention that a dot in the subscript position means summation on that subscript, then $c_{0..} = c_{1..} = 1$.

The observed c_{ijk}'s are corrected for misclassification of the wife's smoking status by first specifying a 4 x 4 matrix of proportionate distribution (Table B-7), where P_{hj} (h,j = 0,1,2,3) is the probability that a subject with true smoking status h will also be observed to have smoking status j. The subscripted notation is shown in Table B-7 for easy reference. $P_{..}$ is equal to unity.

For passive smoking, we are interested only in correcting the c_{i0k} values that are for the observed never-smokers. It is assumed that the P_{hj}'s are the same for cases and controls

(nondifferential misclassification). For given values of wife's subject status (i) and husband's smoking status (k), the correction when the wife's observed smoking status is "never" (j = 0), is:

$$C_{i0k} = c_{i0k} - \sum_{h=j=1}^{3} c_{ijk} \, (p_{h0} / p_{\cdot j}) \qquad \text{(B-1)}$$

where C_{i0k} is the corrected form of the element of the element c_{i0k}. Then the corrected passive risk, RR(c), becomes:

$$RR(c) = C_{101} \times C_{000} / C_{100} \times C_{001} \qquad \text{(B-2)}$$

The values of c_{0jk} in Table B-6 are from prevalence data in the study itself or from a related study, from concordance data, and from each study's data on the smoking prevalence of the never-smokers' husbands. If necessary, the number of former smokers can be estimated from the ever-smokers based on data from nine studies known to us where the percent of both current smokers and former smokers is known (see Table B-16). These data indicate a time trend in nontraditional societies, from 17% former smokers relative to ever-smokers in 1960 to 45% in 1985; we estimate a 20-year lag for the traditional societies such as Hong Kong, China, Japan, and Greece. However, there are no data to support this assumption.

To calculate the individual elements, c_{0jk}, of Table B-6, it is necessary to establish concordance factors--that is, the cross products in 2 x 2 tables of smoking status of husbands and wives by smoking level of the wives. Using data from Sutton (1980), Lee (1987b), Akiba et al. (1986) and Hirayama (1984) and the detailed data in Lee (1987b) on never-smokers, current smokers, and former smokers, we have calculated that an appropriate average concordance factor for current smoking wives and ever-smoking husbands versus never-smoking wives and never-smoking husbands is 3.2; for ever-smoking wives and husbands versus never-smoking wives and husbands, it is 2.8, and for former smoking wives and ever-smoking husbands versus never-smoking wives and husbands, it is 2.2. These concordance factors can be expected to vary from study to study, but the effect of the variability should tend to cancel out as the studies are aggregated. The element $c_{00\cdot}$ and a quantity $s_0 = \sum_{j=1}^{3} c_{0j\cdot}$

are obtained from smoking prevalence data in the study itself, in a related study on the same cohort, or as a last resort from national statistics. The elements $c_{01\cdot}$ and $c_{02\cdot} + c_{03\cdot}$ are taken from the study or are estimated from Table B-16. Element $c_{02\cdot}$ is estimated to be 10% of $(c_{02\cdot} + c_{03\cdot})$; $c_{03\cdot}$ is 90%. Elements c_{000} and c_{001} are obtained from $c_{00\cdot}$ and the proportion of never-smoking controls in the study who are married to either never-smokers or ever-smokers. Elements c_{010} and c_{011} are obtained by solving the equations $c_{010} + c_{011} = c_{01\cdot}$ and $c_{000} \times c_{011} / c_{001} \times c_{010} = 2.2$. Terms $s_{00} = \sum_{j=1}^{3} c_{0j0}$ and $s_{01} = \sum_{j=1}^{3} c_{0j1}$ are obtained from the equations $s_{00} + s_{01} = s_0$ and $s_{01} \times c_{000}/c_{001} \times s_{00} = 2.8$. Then $c_{020} + c_{030} = s_{00} - c_{010}$ and $c_{021} + c_{031} = s_{01} - c_{011}$. The values of c_{020} and c_{021} are then assumed to be 10% of $c_{020} + c_{030}$ and $c_{021} + c_{031}$, respectively, and c_{030} and c_{031} are assumed to be 90%.

To obtain the elements for the subject cases (i = 1) in Table B-6, it is necessary first to set up relative risks for the passively exposed (k = 1) and not passively exposed (k = 0) wives by observed smoking status (j = 0,1,2,3). These risks are shown in Table B-8.

In most instances, the relative risk, RR(e), for female ever-smokers can be obtained from the study itself or from a related paper (Table B-9). In a few instances, it is necessary to estimate RR(e) from other studies similar in time and locale. In some papers, a current smoker risk also is given. We assume (based on cotinine measurements) that the misclassified regular smoker risk, $RR(a)_3$, is equal to the self-reported current smoker risk. Where only RR(e) is available, $RR(a)_3$ can be assumed to be equal to 1.24 x RR(e) based on the data in Table B-17. Because occasional smokers have cotinine levels that are 10% to 30% of those of regular smokers, it is assumed that $RR(a)_2 - 1 = 0.20(RR(a)_3 - 1)$, and because the former smokers (j = 1) are said to be, on average, long term (Wald et al., 1986; Lee, 1987b), we have averaged the data of Alderson et al. (1985), Lubin et al. (1984), and Garfinkel and Stellman (1988) for 10+ year former smokers, namely, that $RR(a)_1 - 1 = 0.09\ (RR(a)_3 - 1)$.

The elements RR_{00} and RR_{01} are obtained from the observed passive relative risk in the study and the never-smoking population weights for controls in Table B-6 by solving the equations

$$(RR_{00} \times c_{000}) + (RR_{01} \times c_{001}) = 1.00$$

and

$$RR_{01} / RR_{00} = RR(p)_0.$$

Other assumptions regarding passive risks can be used for j = 1,2, and 3. We have assumed, based on the data in Varela (1987) who found that 242 long-term former smokers had essentially the same passive risk as 197 never-smokers, that the passive risk for former smokers to be the same as for never-smokers, namely, that $RR(p)_1 = RR(p)_0$. It is also assumed that there is no passive risk for current or occasional smokers so $RR(p)_2$ and $RR(p)_3$ are unity.

Crude versions of the elements c_{1jk} (i = 1 for cases) are obtained by multiplying each element c_{0jk} by its respective RR_{jk}. These are then normalized to give

$$c_{1jk} = \frac{c_{0jk} RR_{jk}}{\sum_{j=0}^{3} \sum_{k=0}^{3} c_{0jk} RR_{jk}}$$

The next step is to set up Table B-7, which is the table of proportionate distribution. This is done by multiplying the observed misclassification rates $(P_{h0}/P_{\cdot j})$ from footnotes 2 and 4 in Tables B-3 and B-4, respectively, by the appropriate elements from Table B-6. For example, $P_{10} = C_{01} \cdot (P_{10}/P_{\cdot 1})$. An attempt was made to use the true misclassification rates from Tables B-3 and B-4 on the theory that they would exhibit less variability in being transferred from the cotinine and discordant answer studies to the passive smoking calculations. However, the method is laborious and, as is shown in the Correa example below, does not lead to increased accuracy.

The next step is to develop a deletions table to implement Equation B-1, above, using the control and case smoking prevalences in Table B-6 and the proportionate distribution in Table B-7. Each observed element, c_{i0k}, in Table B-6 is multiplied by its appropriate observed misclassification factor, $P_{h0} / P_{\cdot j}$, where h = j, to yield a deletion element to be subtracted from the appropriate observed wives' never-smoking-status elements: c_{000}, c_{001}, c_{100}, and c_{101}, to obtain corrected elements C_{000}, C_{001}, C_{100} and C_{101}. Thus, $C_{000} = c_{000} - \sum_{h=j=1}^{3} c_{0j0} P_{h0}/P_{\cdot j}$, etc.

Once these corrected never-smoker elements are obtained, the relative risk corrected for smoker misclassification is obtained from Equation (B-2); $RR(c)_0 = C_{101} \times C_{000}/C_{100} \times C_{001}$, and the bias becomes $RR(p)_0 / RR(c)_0$.

B.6. NUMERICAL EXAMPLE

Using the Correa study as an example, the study tells us that 52.8% of the wives never smoked and that 45.9% of the never-smoking wives were exposed to their spouses' smoke. This establishes $c_{00\cdot}$ as 0.528 and c_{000} and c_{001} as 0.286 and 0.242, respectively. The quantity $s_{0\cdot}$, the proportion of ever-smokers, by difference is 0.472. Assuming (from Table B-16) that the former smokers are 35.5% of the ever-smokers, the former smokers, $c_{01\cdot}$, become 0.167, and the current smokers ($c_{02\cdot} + c_{03\cdot}$) become 0.305. The current smokers are divided into current regular smokers at 90% ($c_{03\cdot} = 0.275$) and current occasional smokers at 10% ($c_{02\cdot} = 0.030$). These data are shown in the bottom line of Table B-10.

Using the concordance factor of 2.8 for ever-smokers versus never-smokers, it is possible to show algebraically that 33.2% of the females in the Correa study would be ever-smoker wives with smoking husbands (s_{01}) and that 14.0% would be ever-smoker wives with never-smoking husbands (s_{00}). Similarly, using the concordance factor of 2.2 for former smoking wives and ever-smoking husbands versus the never-smokers, the former smoking wives married to ever-smoking husbands (c_{011}) would be 10.9% of the total and those married to the never-smoking husbands (c_{010}) would be 5.8%. Then by difference, exposed current smoking wives ($c_{021} + c_{031}$) would be 22.3%, to be split into 20.1% regular smokers (c_{031}) and 2.2% occasional smokers (c_{021}), and the nonexposed current smoking wives ($c_{020} + c_{030}$) would be 8.2%, split into 7.4% regular smokers (c_{030}) and 0.8% occasional smokers (c_{020}). These data now supply all the elements needed in Table B-10 and the control part of Table B-6.

The relative risk for passive smoking, $RR(p)_o$, for females is 2.07 (Correa et al., 1983). The age- and sex-adjusted relative risk for current smoking from a related paper (Correa, 1984) is 12.6. The ratio of female smoking crude risk to the average for males and females is about 80%, indicating an age-adjusted current female risk of about 10. (Note: This is different from the current smoker relative risk that would be calculated from the crude ever-smoker risk of 12.4 used in Table 5-7 [of this report] and Table B-3. The adjusted risk is used here simply as an example.) With these inputs and the weights of controls in the study, the various exposed and nonexposed relative risks are those shown in Table B-11. The weighted average risk for the occasional smokers is calculated as 0.20 (current regular risk - 1) + 1, which for this example is 0.20 (10 - 1) + 1 = 2.80. The weighted average risk for former smokers is 0.09 (current regular risk - 1) + 1, which is 0.09 (10 - 1) + 1 = 1.81. The weighted average risks are split between never-smoking and ever-smoking husbands by

using the passive risks and the population weights. A crude case prevalence table is then made up (Table B-12) by multiplying each c_{0jk} by its respective RR_{jk}. This table is then normalized by dividing through by 3.665 to yield Table B-13, which is the lower half of Table B-6 for this example.

The proportionate distribution table (Table B-14) is developed, as described above, from the misclassification factors in Tables B-3 and B-4 and the bottom line of Table B-10. For example, to arrive at element (h = 3, j = 0) the observed $P_{\cdot 3}$ of 0.275 is multiplied by an observed misclassification factor of 0.0102 (from Table B-3 of this report) to yield 0.00281, which rounds to 0.003. To explore the value of using the true misclassification factors instead of the observed ones, the true and observed m's were carried to five decimal places. An approximation procedure to determine the true smoking probabilities $P_{0\cdot}$, $P_{1\cdot}$, $P_{2\cdot}$, and $P_{3\cdot}$ was carried through four stages. The resulting total true distribution of smoking status, 0.49987, 0.18040, 0.03893, and 0.28081, rounded to three decimal places is essentially identical to the distribution shown in the bottom line of Table B-14. Similarly, any differences in the individual elements were very small and beyond the accuracy of the underlying data. The Correa study was chosen as our example because the female ever-smoking prevalence is reasonably high (47.2%) and the female current smoker lung cancer relative risk is high (10), both factors that should lead to a greater rather than a smaller correction to the passive risk.

We now can set up a deletions table, Table B-15, which is the equivalent of Equation 1 above, by multiplying the control and case elements in Table B-10 and B-13 by the appropriate observed misclassification rates $P_{h0}/P_{\cdot j}$ (h = j), namely, $P_{10}/P_{\cdot 1} = 0.117$, $P_{20}/P_{\cdot 2} = 0.196$, and $P_{30}/P_{\cdot 3} = 0.01020$. For example, to get 0.00678, one multiplies 0.058 from Table B-10 by 0.117. Then the first three columns are summed horizontally to get the fourth column which is then subtracted from the elements in the "never" columns of Tables B-10 and B-13 (column 5) to get the "corrected never" elements (column 6).

The corrected passive risk is now obtained by taking the cross product from the "corrected never" column: 0.07516 x 0.27690/0.04705 x 0.22308 = 1.984, which is to be compared with the observed risk of 2.07. The bias is then 2.07/1.984 = 1.044. It is interesting to note how sensitive the bias is to the smoker relative risk that is assumed. When the crude smoker risk (no age adjustment) of 12.4 for ever-smokers, equivalent to about 15.4 for current regular smokers, is assumed, the corrected passive risk is 1.90, and the basis is twice as great at 1.09.

Table B-1. Observed ratios of occasional smokers to current smokers (based on cotinine studies)

	Females			Both Sexes[3]		
Study	Occ'l	Current	Occ'l/Current	Occ'l[1]	Current	Occ'l Current
Lee (1986)	4	72	0.056	12	176	0.068
Coultas et al. (1988)				59	278	0.212
Haddow et al. (1986)	10	64	0.156			
Feyerabend (1982)[2]				7	82	0.085
Jarvis (1987)				12	90	0.133
Pojer (1984)				25	187	0.134
Wald et al. (1984)				13	131	0.099
Overall	14	136	0.103	128	944	0.136

[1] Occasional smokers are defined as persons who have cotinine levels in body fluids that are between 10% and 30% of the mean of all self-reported current smokers.

[2] The Feyerabend (1982) data are for nicotine.

[3] The "Both Sexes" data are shown to indicate that the female value of 10.3% is not unduly high.

Table B-2. Differences in smoker misclassification bias between EPA estimates and those of P.N. Lee regarding passive smoking relative risks for females

Study	% of U.S. Weight	Lee (1991 Model)[1]			Wells-Stewart Model					
		Lee (1991) Input Parameters			Lee (1991) Input[2] Parameters			EPA Input Parameters (Table 5-7)[2]		
		RR_o	RR_c	Bias	RR_o	RR_c	Bias	RR_o	RR_c	Bias
FONT	35	1.32	1.17	1.13	1.32	1.14[3]	1.15	1.29	1.26[3]	1.03
GARF (Coh)	25	1.17	1.02	1.15	1.17	0.99[4]	1.19	1.17	1.15[4]	1.02
GARF	15	1.23	1.09	1.13	1.23	1.06[5]	1.17	1.31	1.24[5]	1.06
JANE	10	0.75	0.65	1.15	0.75	0.62[6]	1.22	0.86	0.78[6]	1.10
CORR	3	2.07	1.63	1.26	2.07	1.47[7]	1.41	2.07	1.90[7]	1.09

Note: Calculated bias is very sensitive to three key factors, high values of which will drive the bias up; namely, fraction of observed never smokers misclassified, female active smoker relative risk and female smoking prevalence. Lee's inputs are higher than EPA's as indicated in footnotes 2-7. RR_o = observed passive risk. RR_c = passive risk corrected for smoker misclassification bias. Bias = RR_o/RR_c.

[1] Multiplicative model, Lee's Table 3.

[2] EPA's misclassification factors developed in Section B.4., namely, 1.02% of current regular smokers, 19.6% of current occasional smokers, and 11.7% of ex-smokers, when weighted for their respective prevalence and relative risk, are equivalent to about 1.5% of average self-reported ever smokers. EPA used these rates for all studies except FONT which is a special case. Lee used 2.0% for all studies.

[3] All current smokers, regular plus occasional, were eliminated from the analysis based on cotinine test data. This results in a misclassification factor of 0.5% of ever smokers. Lee's 49% ever smokers is higher than 1985 U.S. statistics value of 42%.

Table B-2. (continued)

[4] A female smoker risk of 3.58 (U.S. DHHS, 1986) and smoker prevalence of 32% (Hammond, 1966) are considered standard for this study. Lee used 8.0 and 49%.

[5] EPA estimates a smoker risk of 6 and a smoking prevalence of 46% for the time period 1971-81 vs. Lee's values of 8.0 and 49%.

[6] The main difference is in the assumed smoker misclassification rate but Lee's assumption of 49% smoking prevalence vs. 46% assumed by EPA increases the bias estimate by about 3%.

[7] Lee assumed 58% smoking prevalence vs. 47% which EPA got from the paper itself. Lee assumed a lower smoker risk (9.5) vs. EPA's 12.4; the effect of this was offset by Lee's assumption of a multiplicative model for smoker's passive risk vs. EPA's assumption of no passive risk for smokers.

Table B-3. Misclassification of female current smokers

		Self-reported Smoking Status		
Study	Cotinine Level[1]	Never[2]	Former[2]	Current
Coultas et al. (1988)	10-30	7	3	
	30+	5	8	
	All	387	79	184
Cummings (1990)	10-30	0	1	
	30+	2	0	
	All	225	143	116
Pierce et al. (1987)	10-30	9	4	
	30+	3	3	
	All	232	79	167
Subtotal	10-30	16	8	(67% never)
	30+	10	11	(48% never)
	All	844	301	467
Lee (1986)[3]	10-30	3	2	
	30+	2	3	
	All	333	125	256
Haddow et al. (1986)[3]	10-30	1	1	
	30+	0	1	
	All	174	58	64
Haddow et al. (1988)[3]	10-30	8	4	
	30+	1	0	
	All	1,128	380	503
Riboli (1991)[3]--US[4]	10-30	1	0	
	30+	0	0	
	All	224	81	143
Riboli (1991)[3]--East Asia[5]	10-30	1	1	
	30+	1	0	
	All	325	25	77
Riboli (1991)[3]--Greece[6]	10-30	0	0	
	30+	0	0	
	All	96	5	15
Total	10-30	30	16	
	30+	14	15	
	All	3,124	975	1,525

05/21/92

2501032262

Table B-3. (continued)

[1] Cotinine levels are in units of percents of the mean of self-reported smokers for each study; 30+% are defined as current regular smokers, 10-30% are occasional smokers.

[2] The observed current smokers are assumed to be 90% regular (1,372) and 10% occasional (153) smokers. For regular smokers, misclassification as never-smokers is 14/372 = 1.02% of observed current regulars or 14/(1,372 + 14 + 15) = 1.00% of true current regulars. For occasional smokers, misclassification is 30/153 = 19.6% of observed current occasionals or 30/(153 + 30 +16) = 15.1% of true current occasionals. For current smokers misclassified as former smokers the factors are 15/1,372 = 1.09% for observed and 15/1,401 = 1.07% for true regular smokers, and 16/153 = 10.5% for observed and 16/199 = 8.0% for true occasionals.

[3] For Lee (1986), Haddow et al. (1986), Haddow et al. (1988), and Riboli (1991), there was no breakdown given between "Never" and "Former", because the numbers are small, an estimate was made based on the subtotal distribution. The number of smokers had to be estimated in some cases.

[4] New Orleans, Los Angeles, and Honolulu.

[5] China (Shanghai), Hong Kong, and Japan (Sendai).

[6] Athens.

Table B-4. Misclassification of female former smokers reported as never-smokers based on discordant answers

Study	Locale	Former Smokers (FS)[1]	Ever-Smokers (ES)[1]	Reported never-smokers who reported earlier that they had smoked[1]		
				N	Percent of ES	Percent of FS
Kabat and Wynder (1984)[5]	U.S.					
Controls		109	319	0	0.0	0.0
Cases		222	652	7	1.1	3.2
Machlin et al. (1989)	U.S.	194	687	52	7.6	26.8
Krall et al. (1989)[2]	Mass.	11	30	1	3.3	9.1
Britten (1988)[3]	U.K.	320	878	38	4.3	11.9
Lee (1987b)	U.K.	85	243	13	5.5	15.3
Akiba et al. (1986)	Japan	8	38	0	0.0	0.0
Overall[4]		949	2847	111	3.9	11.7

[1] Number of former smokers and ever-smokers had to be estimated in some cases.
[2] Krall data are based on 20-year recall.
[3] Britten data include only those persons who said they never smoked but actually had smoked regularly one or more cigarettes per day.
[4] For former smokers, misclassification as never-smokers would appear to be 111/949 = 11.7% of observed former smokers or 111/(949 + 111) = 10.5% of true former smokers, but from Table B-3 16 + 15/(16 + 15 + 975) = 3.08% of former smokers are really current smokers, so the 949 + 111 = 1,060 should be reduced by 3.08% to 1,027 as the number of true former smokers. Then 111/1,027 = 10.81% based on true former smokers.
[5] Dr. Kabat (private communication) advised that of 13 misclassifieds, 8 were females, 1 of whom used snuff.

Table B-5. Misclassification of female lung cancer cases

Source	Number of Ever-smokers	Number Misclassified
CHAN Chan et al. (1979)[1]	12	1
KABA Kabat and Wynder (1984)[2]	652	7
AKIB Akiba et al. (1986)	38	0
PERS Pershagen et al. (1987)	179	2
HUMB Humble et al. (1987)[3]	223	1
Total	1,104	11 (1%)
General Population[4]	1,838	104 (5.7%)

[1] Chan sampled five Type I and II never-smokers, one of whom was said by a relative to have smoked a few hand-wrapped cigarettes for a year at age 71. The ratio of smoking to nonsmoking cases for Types I and II was 44/19, which, multiplied by 5, leads to 12 estimated ever-smokers.
[2] Dr. Kabat (private communication) advised that of 13 misclassifieds, 8 were females, 1 of whom used snuff.
[3] Of the four misclassifieds found, Dr. Humble (private communication) has advised that most if not all were males. We have assumed one female.
[4] The general population data are taken from the four nonlung cancer cohorts in Table B-4, namely, Machlin (1989), Krall (1989), Britten (1988), and Lee (1987b).

Table B-6. Notation for proportionate distribution of reported female lung cancer cases and controls by husband's smoking status

		Wife's Observed Smoking Status (j)				
Wife's Subject Status (i)	Husband's Smoking Status (k)	Never (j = 0)	Ex (j = 1)	Occ'l (j = 2)	Reg (j = 3)	Total
Control	Never (k = 0)	c_{000}	c_{010}	c_{020}	c_{030}	$c_{0\cdot 0}$
(i = 0)	Ever (k = 1)	c_{001}	c_{011}	c_{021}	c_{031}	$c_{0\cdot 1}$
	Total	$c_{00\cdot}$	$c_{01\cdot}$	$c_{02\cdot}$	$c_{03\cdot}$	$c_{0\cdot\cdot}$ (= 1)
Case	Never (k = 0)	c_{100}	c_{110}	c_{120}	c_{130}	$c_{1\cdot 0}$
(i = 1)	Ever (k = 1)	c_{101}	c_{111}	c_{121}	c_{131}	$c_{1\cdot 1}$
	Total	$c_{10\cdot}$	$c_{11\cdot}$	$c_{12\cdot}$	$c_{13\cdot}$	$c_{1\cdot\cdot}$ (= 1)

Table B-7. Proportionate distribution notation for subjects by observed and true smoking status

Wife's Observed Smoking Status (j)	Wife's True Smoking Status (h)				
	Never (h = 0)	Former (h = 1)	Occ'l (h = 2)	Reg. (h = 3)	Total
Never (j = 0)	P_{00}	P_{10}	P_{20}	P_{30}	$P_{\cdot 0}$
Former (j = 1)	P_{01}	P_{11}	P_{21}	P_{31}	$P_{\cdot 1}$
Occ'l (j = 2)	P_{02}	P_{12}	P_{22}	P_{32}	$P_{\cdot 2}$
Reg. (j = 3)	P_{03}	P_{13}	P_{23}	P_{33}	$P_{\cdot 3}$
Total	$P_{0\cdot}$	$P_{1\cdot}$	$P_{2\cdot}$	$P_{3\cdot}$	$P_{\cdot\cdot}(= 1)$

Table B-8. Observed lung cancer relative risks for exposed and nonexposed wives by the wife's smoking status using average never-smoking wives as the reference category

	Wife's Smoking Status			
Husband's Smoking Status	Never ($j = 0$)	Former ($j = 1$)	Occ'l ($j = 2$)	Reg. ($j = 3$)
Never ($k = 0$)	RR_{00}	RR_{10}	RR_{20}	RR_{30}
Ever ($k = 1$)	RR_{01}	RR_{11}	RR_{21}	RR_{31}
Weighted avg. active risk	$RR(a)_0 = 1.00$	$RR(a)_1$	$RR(a)_2$	$RR(a)_3$
Passive risk[1] $RR(p)_j = RR_j1/RR_{j0}$	$RR(p)_0$	$RR(p)_1$	$RR(p)_2$	$RR(p)_3$

[1] Observed passive risk--the ratio of the exposed risk to the unexposed risk in each column.

Table B-9. Prevalences and estimates of lung cancer risk associated with active and passive smoking[33]

	Ever-smokers		Never-smokers		
Case-Control	Prev. (%)[1]	Crude RR[2]	Prev. of Exposed (%)[3]	Crude RR[2, 17]	Adj. RR[2, 4, 17]
AKIB	21	2.38 (1.67, 3.39)	70	1.52 (0.96, 2.41)	**1.5 (1.0, 2.5)**
BROW	29	4.30[23] (2.24, 8.24)	15	**1.52[23] (0.49, 4.79)**	*
			12	1.82[23] (0.45, 7.36)[7]	1.68[23] (0.39, 6.90)[7]
BUFF	59	7.06[15] (5.18, 9.63)	84	**0.81[15] (0.39, 1.66)**	*
CHAN	26	3.48 (2.42, 4.99)	47	**0.75 (0.48, 1.19)**	*
CORR	47	12.40 (8.35, 18.4)	46	**2.07[24] (0.94, 4.52)**	*
FONT[34]	42[21]	8.0[21]	63	1.37 (1.10, 1.69)	**1.29 (1.03, 1.62)**
			66	1.21 (0.94, 1.56)	1.28 (0.98, 1.66)
			64	1.32 (1.08, 1.61)	*
GAO	18	2.54 (2.06, 3.12)	74	**1.19 (0.87, 1.63)**	1.34[5,6]
GARF	*	*	61	**1.31 (0.93, 1.85)**	1.70[26] (0.98, 2.94)[7]
GENG	41	2.77[27] (1.89, 4.07)	44	**2.16** (1.21, 3.84)	*
HIRA[8]	16	3.20[9] (2.67, 3.83)	77	**1.53[5] (1.10, 2.13)**	1.64[5] *
HUMB	41	16.3 (10.5, 25.1)	56	2.34 (0.96, 5.69)	**2.2 (0.9, 5.5)**
INOU	16	1.66 (0.73, 3.76)	64	2.55[16] (0.90, 7.20)	2.54[5,10] *

2501032269

Table B-9. (continued)

	Ever-smokers		Never-smokers		
Case-Control	Prev. (%)[1]	Crude RR[2]	Prev. of Exposed (%)[3]	Crude RR[2,17]	Adj. RR[2,4,17]
JANE	46[21]	8.0[21]	80	0.86 (0.57, 1.29)	0.93/0.44[11]
KABA[28]	42	5.90 (4.53, 7.69)	60	0.79 (0.30, 2.04)	*
KALA	17	3.32 (2.12, 5.22)	60	1.62[12] (0.99, 2.65) 1.41 (0.78, 2.55)	1.92 (1.02, 3.59)[7] *
KATA	28	1.21 (0.50, 2.90)	82	*[19]	*
KOO	32	2.77 (1.96, 3.90)	49	1.55 (0.98, 2.44)	1.64
LAMT	24	3.77 (2.96, 4.78)	45	1.65 (1.22, 2.22)	*
LAMW	22	4.12 (2.79, 6.08)	56	2.51[20] (1.49, 4.23)	*
LEE	60[29]	4.61[29]	68	1.03 (0.48, 2.20)	0.75/1.60[13]
LIU	0.05	*	87	0.74 (0.37, 1.48)	0.77 (0.35, 1.68)
PERS	37[21]	4.2[21]	43	1.28 (0.82, 1.98)	1.2 (0.7, 2.1)[7]
SHIM	21[21]	2.8[21]	56	1.08[30] (0.70, 1.68)	*
SOBU	21	2.81 (2.22, 3.57)	54	1.06[12] (0.79, 1.44) 1.77 (1.29, 2.43)	1.13[12] (0.78, 1.63)[7] 1.57 (1.07, 2.31)[7]
SVEN	43	5.97 (4.11, 8.67)	66	1.26[14] (0.65, 2.48)	1.4[14]
TRIC	10	2.81[25] (1.69, 4.68)	52	2.08[25] (1.31, 3.29)	*

2501032270

Table B-9. (continued)

	Ever-smokers		Never-smokers		
Case-Control	Prev. (%)[1]	Crude RR[2]	Prev. of Exposed (%)[3]	Crude RR[2,17]	Adj. RR[2,4,17]
WU	58	4.38 (2.97, 6.47)	60	**1.41[18] (0.63, 3.15)**	1.2 (0.6, 2.5)[7]
WUWI	37	2.24 (1.92, 2.62)	55	**0.79 (0.64, 0.98)**	0.7
BUTL (Coh)	14[21]	4.0[21]	*	2.45[31]	**2.02 (0.48, 8.56)[7]**
GARF (Coh)	33[22]	3.5[22]	72	*	**1.17[5] (0.85, 1.61)[7]**
HIRA (Coh)	16	3.20[9] (1.96, 3.90)	77	**1.38 (1.03, 1.87)**	1.61 *
HOLE[32] (Coh)	56	4.2[21]	73	2.27 (0.40, 12.7)	**1.99 (0.24, 16.7)[7]**

1 Percent ever-smokers in controls of whole study (or parent study).
2 Parentheses contain 90% confidence limits, unless noted otherwise. Crude ORs and their confidence limits were calculated by the reviewers wherever possible. Boldface indicates values used for analysis in text of this report. OR for case-control studies; relative risk (RR) for cohort studies. The reference category for active smoking is all never-smoking, for passive smoking, it is unexposed never-smokers.
3 Percent of never-smoking controls exposed to spousal smoking, unless noted otherwise.
4 Calculated by a statistical method that adjusts for other factors (see Table 5-5).
5 Composite measure formed from categorical data at different exposure levels.
6 For Gao, data are given as (number of years lived with a smoker, adj. OR): (< 20, 1.0), (20-29, 1.1), (30-39, 1.3), (40+, 1.7).
7 95% confidence interval.
8 Case-control study nested in the cohort study of Hirayama. OR for ever-smokers is taken from cohort study (shown in table below). This case-control study is not counted in any summary results where HIRA(Coh) is included.
9 Crude OR is calculated from prospective data in Hirayama (1988). Adjusted OR for ever-smokers given there is 2.67 (no confidence interval [C.I.]).
10 For Inoue, data are given as (number of cig./day smoked by husband, adj. OR): (< 19, 1.58), (20+, 3.09).
11 From subject responses/from proxy responses.
12 For the first value, "ETS exposed" means the spouse smokes; for the second value, "ETS exposed" means a member of the household other than the spouse smokes.
13 From subject responses/from spouse responses.
14 Exposure at home and/or at work.

Table B-9. (continued)

[15] Exposure to regularly smoking household member. Differs slightly from published value of 0.78, wherein 0.5 was added to all exposure cells.

[16] OR reported in study is 2.25, in contrast to the value shown that was reconstructed from the confidence intervals reported in the study; no reply to inquiry addressed to author had been received by press time.

[17] ORs for never-smokers applies to exposure from spousal smoking, unless indicated otherwise.

[18] Raw data for WU is from Table 11 of the Surgeon General's report (U.S. DHHS, 1986). Data apply to adenocarcinoma only.

[19] Odds ratio is not defined because number of unexposed subjects is 0 for cases or controls.

[20] Table entry is for exposure to smoking spouse, cohabitants, and/or coworkers; includes lung cancers of all cell types. The OR for spousal smoking alone is for adenocarcinoma only: 2.01 (90% C.I. = 1.20, 3.37).

[21] From other studies similar in location and time period (see Table 5-7).

[22] Prevalence is calculated from figures in Stellman and Garfinkel (1986) and includes all women except those who "never smoked regularly." RR is from U.S. Surgeon General (U.S. DHHS, 1982).

[23] Adenocarcinoma only. Data and OR value communicated from author (Brownson).

[24] Excludes bronchioalveolar carcinoma. Crude OR with bronchioalveolar carcinoma included is reported to be 1.77, but raw data for calculation of confidence interval are not provided.

[25] Known adenocarcinomas and alveolar carcinomas were excluded, but histological diagnosis was not available for many cases. Data are from Trichopoulos et al. (1983).

[26] Estimate for husband smoking 20 cigarettes per day.

[27] Crude OR reported in study is 3.05 (95% C.I. = 1.77, 5.30); adjusted OR is 2.6(95% C.I. = 1.4, 4.6).

[28] For second KABA study (see addendum in study description of KABA), preliminary unpublished data and analysis based on ETS exposure in adulthood indicate 68% of never-smokers are exposed and OR = 0.90 (90% C.I. = 0.51, 1.58), not dissimilar from the table entry shown.

[29] From Alderson et al. (1985).

[30] From crude data estimated to be the following: exposed cases 52, exposed controls 91, unexposed cases 38, unexposed controls 72.

[31] RR is based on person-years of exposure to spousal smoking. Prevalence in those units is 20%.

[32] RR values under never-smoker are for lung cancer mortality. For lung cancer incidence, crude RR is 1.51 (90% C.I. = 0.41, 5.48) and adj. RR is 1.39 (95% C.I. = 0.29, 6.61).

[33] Values used for inference in this report are shown in boldface. * means no information available.

[34] The first, second, and third entries are calculated for population controls, colon cancer controls, and both control groups combined, respectively. For adenocarcinoma alone, the corresponding ORs, both crude and adjusted, are higher by 0.15 to 0.18.

Table B-10. Observed smoking prevalence among the controls--Correa example

Husband's Smoking Status	Wife's Smoking Status: Never	Former	Occasional	Regular	All
Never	0.286	0.058	0.008	0.074	0.426
Ever	0.242	0.109	0.022	0.201	0.574
All	0.528	0.167	0.030	0.275	1.000

Table B-11. Observed relative risks--Correa example

Husbands' Smoking Status	Wife's Smoking Status: Never (j = 0)	Former (j = 1)	Occasional (j = 2)	Regular (j = 3)
Never	0.67	1.07	2.80	10.0
Ever	1.39	2.21	2.80	10.0
Weighted Average	1.00	1.81	2.80	10.0
Passive Risk, $RR(p)_j$	2.07	2.07[1]	1.00[1]	1.00[1]

[1] Assumed.

Table B-12. Crude case table - prevalence of cases by smoking status--Correa example

	Wife's Smoking Status				
Husband's Smoking Status	Never	Former	Occasional	Regular	All
Never	0.192	0.062	0.022	0.740	1.016
Ever	0.336	0.241	0.062	2.010	2.649
All	0.528	0.303	0.084	2.750	3.665

Table B-13. Normalized case table - prevalence of cases by smoking status--Correa example

	Wife's Smoking Status				
Husband's Smoking Status	Never	Former	Occasional	Regular	All
Never	0.052	0.017	0.006	0.202	0.277
Ever	0.092	0.066	0.017	0.549	0.723
All	0.144	0.083	0.023	0.750	1.000

Table B-14. Proportionate distribution of observed and true smoking status for wives in Correa example[1]

	Wife's True Smoking Status				
Wife's Observed Smoking Status	Never (h = 0)	Former (h = 1)	Occasional (h = 2)	Regular (h = 3)	All
Never (j = 0)	0.500	0.020	0.006	0.003	0.528
Ex (j = 1)	0	0.161	0.003	0.003	0.167
Occ'l (j = 2)	0	0	0.030	0	0.030
Regular (j = 3)	0	0	0	0.275	0.275
All	0.500	0.180	0.039	0.281	1.000

[1] Values rounded to three decimal places.

Table B-15. Deletions from the never columns in Tables B-10 and B-13

Husband's Smoking Status		Wife's Smoking Status Former (1)	Occ'l (2)	Regular (3)	Sum[1] (4)	Observed Never (5)	Corrected Never[2] (6)
Table B-10 (pop.)	Never	0.00678	0.00157	0.00075	0.00910	0.286	0.27690
	Ever	0.01274	0.00433	0.00205	0.01892	0.242	0.22308
Table B-13 (cases)	Never	0.00198	0.00120	0.00206	0.00524	0.05229	0.04705
	Ever	0.00769	0.00331	0.00559	0.01659	0.09178	0.07519

[1] (4) = (1) + (2) + (3)
[2] (6) = (5) - (4)

Table B-16. Observed ratios of female former smokers to ever-smokers in the U.S.A., U.K., and Sweden: populations or controls (numbers or %)

Study	Time Frame	Never-Smokers	Current Smokers	Former Smokers	Ever-Smokers	Former/Ever-Smokers
Hammond (1966)	1960	381,369	150,017	31,285	181,302	0.17
Buffler et al. (1984)	1978	41%	38%	21%	59%	0.36
Wu et al. (1985)	1980	92	73	55	128	0.43
Lee (1987b)	1980	48.3%	33.6%	18.1%	51.7%	0.35
Brownson et al. (1987)	1980	47	11	8	19	0.42
Britten (1988)	1982	767	558	320	878	0.36
Humble et al. (1987)	1982	162	63	48	111	0.43
Svensson et al. (1989)	1984	120	53	36	89	0.40
Garfinkel and Stellman (1988)	1982	350,650	132,366	136,909	269,275	0.51

Assumed Ratios by Years (non-traditional societies)[1]

Year	1960	1965	1970	1975	1980	1985
Ratio	0.17	0.23	0.28	0.34	0.39	0.45

[1] Traditional societies (Japan, Greece, China, Hong Kong) are estimated to lag these ratios by about 20 years, although there are no data in the studies to confirm this. However, because the bias for the traditional societies is very low, changes in values of this parameter have little effect.

2501032277

Table B-17. Observed ratios of current smoker lung cancer risk to ever-smoker risk for females

		Lung Cancer RR		Ratio
Study	Exposed Cases Plus Controls	Current Smoker	Ever-Smoker	Current Smoker RR/ Ever-smoker RR
Alderson et al. (1985)	901	4.5	4.75	0.95
Buffler et al. (1984)	701	7.9	6.9	1.15
Garfinkel and Stellman (1988)	832	12.7	8.35	1.52
Humble et al. (1985)	268	18.0	13.0	1.38
Svensson et al. (1989)	261	8.46	6.10	1.39
Wu et al. (1985)	317	6.5	4.4	1.48
Overall	3,280	8.05	6.52	1.24[1]

[1] The summary ratio of 1.24 is the log mean of the individual ratios weighted by the exposed cases plus controls in that study.

APPENDIX C

REVIEW FORMAT FOR CASE-CONTROL STUDIES

PART I GENERAL

Study name____________________

Location____________________

Time period (data collection)____________________

Study objective(s)____________________

____

____

The source of the primary data set is the current study _____ or a parent study

(ref)____________________

containing CS (current)_____ FS (former) _____ NS (never-smoker) _____

Study uses term "nonsmoker" _____ or "never-smoker" _____ to mean

nonsmoker____________________

____

never-smoker____________________

____

"Exposed" to ETS means (preferably in terms of spousal smoking)

____

____

Recall span (how far back in time ETS-exposure was measured)____________________

____

ETS sources include cigarette _______ cigar _______ pipe _______ other _______

Describe inclusion of non-smoking (never smoking) females not currently married (number of cases and controls, assumptions exposure)

____

____

____

II DATA COLLECTION (includes NS______ FS______ CS______ unless noted)

Inclusion/Exclusion criteria

Cases____

____

____

Controls (include matching variables in PART V)______________________

____

____

Main source of subjects	Cases	Controls
Hospital(s) #__________	______	______
Community	______	______
Other__________	______	______

Incident cases Y________ N________

Control sampling

Cumulative ________ Density ________

Unmatched ________ Matched ________

Method of collection	Cases	Controls
Face-to-face	______	______
Telephone	______	______
Self-admin. ques.	______	______
Medical records	______	______
Vital stat. records	______	______
Other__________	______	______

Collected data verified/corroborated with other sources Y________ N________

DRAFT--DO NOT QUOTE OR CITE

	Cases	Controls
Sample size (prior to attrition)		
females	______	______
males	______	______
Attrition (selection or follow-up)		
females	______	______
males	______	______
Source of response		
subject	______	______
proxy	______	______

Exposure sources NS______ FS______ CS______

	Yes	No
Childhood	______	______
Adulthood	______	______
Spouse	______	______
Parents/in-laws	______	______
Other family/ live-ins	______	______
Workplace	______	______
Other	______	______

Age NS______ FS______ CS______

Distribution	Cases	Controls
______	______	______
______	______	______
______	______	______
______	______	______
Mean	______	______
Standard error	______	______
Standard deviation	______	______
Range	______	______

PART III CLINICAL DATA

Primary lung cancer verified by NS______ FS______ CS______

Histology ______
Cytology ______
Radiology/clinical ______

DRAFT--DO NOT QUOTE OR CITE

Death certificate ______
Tumor registry ______
Mortality records ______
Other____________ ______
Not verified ______

Airway proximity (no. exp cases/no. cases) NS_____ FS_____ CS_____

Central ____________________

Table__________

Peripheral ____________________

Tumor type (no. exp cases/no. cases) NS_____ FS_____ CS_____

Squamous cell ____________________

Table__________

Small cell ____________________

Adenocarcinoma ____________________

Large cell ____________________

Others or unspecified ____________________

PART IV STATISTICAL ANALYSIS (includes NS_____ FS_____ CS_____ unless noted)

Raw data (for analysis)		Cases	Controls
females	unexp	________	________
	exp	________	________
males	unexp	________	________
	exp	________	________

Comments (include measure of exposure) Table __________

2501032282

Unadjusted (crude) analysis

Estimate OR ________ ________% CI (________,________)

Comments Table ________

Test of signif p-value ________

Test for trend p-value ________

Comments Table ________

Adjusted analysis

Estimate OR ________ ________% CI (________,________)

Test of signif p-value ________

Test for trend p-value ________

Comments Table ________

PART V DEPENDENT VARIABLES (potential confouders and effects modifiers considered)

	In Matching	In Analysis	Otherwise
Age			
Gender			
Race/ethnicity			
Hospital			
Residence/ neighborhood			
Housing type			
House/room sizes			
Vital statistics			
Smoking status			
SES			
Medical health			
Menstrual/ reproductive			
Occupation			
Outdoor air pollution			
Cooking habits			
Drinking			
Diet			

DRAFT--DO NOT QUOTE OR CITE

Education			
Family history of LC			
Other indoor smoke/fumes			
Radon			
Lifestyle			
Climate/ ventilation			

2501032284

APPENDIX D. LUNG CANCER MORTALITY RATES ATTRIBUTABLE TO SPOUSAL ETS IN INDIVIDUAL EPIDEMIOLOGIC STUDIES

Many of the epidemiologic studies on lung cancer and environmental tobacco smoke (ETS) were part of larger investigations that included ever-smokers and never-smokers. For those studies, the lung cancer mortality rate (LCMR) for all causes, appropriate to the location and time period of the study, has been obtained from other sources. Those values and parameter estimates from the studies are used to partition the excess LCMR from all causes (i.e., the excess after allowance for baseline sources) into components attributable to ever-smokers (from current and former smoking) and never-smokers (from exposure to spousal ETS) and to estimate the LCMR in the subpopulations of interest--unexposed never-smokers (meaning not exposed to spousal smoking), exposed never-smokers (exposed to spousal smoking), and ever-smokers ("exposed" is not used to mean exposure to non-spousal ETS, which applies to the whole target population). The method is explained in Sections 6.3.1 and 6.3.2.

Lung cancer mortality rates for the case-accrual periods of case-control studies are displayed in Table D-1. For the studies that collected data on both ever-smokers and never-smokers, the parameter estimates used are shown in Table D-2. The value for the lung cancer mortality rate is from Table D-1, and the remaining estimates are from individual study data. For HIRA(Coh), the lung cancer mortality rate for the time and location of the nested case-control study HIRA is used. For GARF(Coh), the rate for GARF in 1971 is assumed, which is the approximate time of the cohort follow-up. These values may not be very "representative" for lung cancer mortality in these two cohort studies because they extended over several years, and the LCMRs changed from year to year, particularly in the United States. This same difficulty arises in choosing a "representative" year for lung cancer mortality in the case-control studies, although to a lesser degree. The most extreme examples are KABA, PERS, INOU, and GARF with case-accrual periods of 10 years or more.

The estimates of prevalence of ever-smokers and the percent of never-smokers exposed to spousal smoking are the observed proportions in the control group. The extent to which the control group is representative of the country's population differs between studies, with those most questionable shown in Table 5-14A. The study reviews in Appendix A provide more detailed information. The restriction of cell types among cases in some studies is another consideration. Active smoking is much more strongly associated with occurrence of squamous and small cell carcinoma than with large cell carcinoma and adenocarcinoma. FONT presents evidence that passive smoking is more associated with adenocarcinoma than with other cell types. As noted

in Table 5-15, some studies excluded candidate lung cancer cases of specific histopathological types. This may produce some bias and distortion of comparison between studies. For example, BROW includes only cases of adenocarcinoma, which should bias the relative risk of ever-smokers toward unity, thus attributing too little lung cancer mortality to active smoking and too much to passive smoking and background sources.

Of a more positive nature, there is some advantage to using data from a single study to assign attributable *fractions* to different causes. To estimate the yearly number of lung cancers from each cause, the fraction is multiplied by the LCMR for the location and time of the study; that figure has to be obtained from sources on vital statistics. As seen in Table D-2, the mortality rates from lung cancer vary considerably between and within countries. For example, the rates used for studies in the United States range between 9 and 26. Applying the lung cancer rate suitable to each individual study should provide better estimates for comparison within a country than using a single figure for the whole country for some specific year.

Despite the reservations described, partitioning the lung cancer mortality for each study into components attributable to ever-smoking, spousal ETS, and baseline sources (nontobacco smoke and nonspousal ETS) provides a broad overview worth noting. The calculated values are shown in Table D-3. Estimates of relative risk for exposure to spousal ETS (RR_2 in notation of Section 6.3.2) less than 1.0 (see Table 5-8) were replaced by 1.0 to avoid a negative LCMR attributable to spousal ETS and the consequent inflation of the LCMR attributable to baseline sources and ever-smoking. Aside from the studies for Hong Kong and China, estimates of lung cancer mortality due to background sources cluster in the interval 1.5 to 5.5 (excluding BROW, which is strongly biased), predominantly from 3 to 5. The values for Hong Kong and China, however, are much higher, ranging from 7 to 14.5. The presence of indoor sources of non-ETS encountered in some of the studies in China may be a factor, but there is no apparent explanation for the outcome in Hong Kong. Assuming that the background rate of lung cancer is much higher in Hong Kong (and possibly China) as it appears, then the question arises as to whether the high excess rate relative to other countries may be attributable to higher exposure to ETS aside from spousal smoking or whether it is more likely due to other causes. Summary data from the ten-country collaborative study of ETS exposure to nonsmoking women conducted by the International Agency for Research on Cancer (IARC) (Riboli et al., 1991) was kindly submitted to us for Hong Kong, Japan (Sendai), and the United States (Los Angeles, New Orleans) from Drs. L.C. Koo, H. Shimizu, A. Wu-Williams, and T.H. Fontham, respectively. The average cotinine/creatinine (ng/mg) levels for nonsmoking women who are not employed and not married to a smoker are close for Sendai, Los Angeles, and New Orleans, but they are several times higher

for Hong Kong. Consequently, a high contribution to background lung cancer mortality from ETS aside from spousal smoking cannot be eliminated as a factor.

The lung cancer attributable to ever-smoking, spousal smoking, and baseline sources depends on the population proportions for those categories as well as the relative risks. Study estimates of the LCMR in each category, in units of lung cancer deaths per 100,000 at risk per year, are shown in Table D-4. The last two columns show the ratios of the LCMR and the excess LCMR for exposed never-smokers to ever-smokers. As above, relative risk estimates of less than 1.0 were set to 1.0 for the calculations. There is considerable variability across study estimates, even within the same country, as observed previously in the relative risks for spousal smoking.

To summarize, for studies that included data on ever-smokers, the LCMR for all causes was partitioned by attributable source (Table D-3). Although there is considerable uncertainty in the estimates from statistical variability and other sources, the outcomes provide some useful gross comparisons. For example, the lung cancer mortality rates from all causes differ markedly between countries and also vary widely between studies within the United States. The proportion of lung cancers attributable to ever-smoking is very high in the United States, compared to some more traditional countries (e.g., Japan and Greece).

Individual study estimates of the number of lung cancer deaths per year per 100,000 of female population from exposure of never-smokers to spousal ETS are predominantly between 0 and about 2.5. Estimates of the LCMR attributable to baseline sources (nonspousal ETS and nonsmoking causes) are somewhat higher, largely between 2 and 5, except in Hong Kong and China, where they range between 7+ and 14. (The U. S. study denoted as BROW has a high value, but that should be upwardly biased because it used only cases of adenocarcinoma, which is not a common cell type in smokers.) For reasons discussed in Chapter 5, we would be reluctant to draw conclusions about China on the basis of the epidemiologic studies. The evidence from Hong Kong, however, is very suggestive that the lung cancer rate in women due to baseline sources is very high. The extent to which that is attributable to nonsmoking sources of lung cancer and/or high exposure to nonspousal ETS is not apparent. The cotinine data for Hong Kong from the ten-country IARC study (Riboli, 1990) is consistent with excessively high ETS exposure, so nonspousal ETS may be a factor.

Table D-1. Female lung cancer mortality from all causes in case-control studies[1]

Study	Location	Case Accrual	Begin	Average	End	Accrual -10 yrs Average	Accrual -20 yrs Average
AKIB	Japan	1971-80	5.13	6.05	7.08	4.57	2.30
BROW	USA	1979-82	15.68	17.29	19.09	9.49	4.75
BUFF	USA	1976-80	13.94	15.29	17.20	7.86	4.38
CHAN	HK	1976-77	23.59	23.59	23.59	19.05	*
CORR[2]	USA	1979-82	26.0	26.0	26.0	9.49	4.75
GAO[3]	China	1984-86	*	18.0	*	14.3[2]	5.1[2]
GARF	USA	1971-81	9.45	13.55	17.20	6.87	*
GENG[3]	China	1983	*	27.8	*	13.8[2]	*
HIRA[7]	Japan	1965-81	4.46	5.70	7.08	4.01	*
HUMB[2]	USA	1980-84	17.7	17.7	*	10.55	5.13
INOU	Japan	1973-83	5.55	6.53	7.46	4.93	2.95
JANE[2]	USA	1982-84	23.7	23.7	*	9.06	5.42
KABA[4]	USA	1961-80	4.69	13.20	17.20	6.61	4.16
KALA[4]	Greece	1987-89	6.58	6.58[4]	6.58	6.75	5.83[4]
KATA[4]	Japan	1984-87	*	7.46[4]	*	4.66	2.26
KOO	HK	1981-83	22.34	22.61	22.75	19.82	*
LAMT[4]	HK	1983-86	22.75	23.46	23.69	21.33	*
LAMW	HK	1981-84	22.34	22.88	23.69	20.09	*
LEE	Eng/Wal	1979-82	16.28	17.11	17.89	12.60	8.1
PERS[4]	Sweden	1961-80	3.71	5.09	7.56	3.95[4]	*
SHIM[4]	Japan	1982-85	7.46	7.46[4]	7.46	5.65	4.28
SOBU[4]	Japan	1986-88	7.46	7.46[4]	7.46	6.36	4.93
SVEN[4]	Sweden	1983-85	7.72	7.72[4]	7.72	5.78	3.80
TRIC	Greece	1978-80	6.88	6.40	5.99	5.75	5.31[5]
WU	USA	1981-82	17.20	18.15	19.09	10.14	4.96
WUWI[6]	China	1985-87	*	11.6	*	9.2[2]	*

[1] Rates are per 100,000 per year. Annual rates for 2-year periods from Kurihara et al. (1989) were averaged over the years cases were accrued for each study unless otherwise noted. Where part (or all) of the accrual period fell 1 or 2 years outside the years for which rates were available, rates from the nearest 2-year period available were assumed to apply to the missing years. U.S. rates are for white females only.

[2] Data for accrual period from 1978-82 rates in IARC (1987), standardized to 1950 world population from Kurihara et al. (1989). For Correa, weighted average of white and black rates; for Humble, weighted average of Hispanic and non-Hispanic white rates.

Table D-1. (continued)

[3] Accrual period data for Gao and Geng derived from IARC (1987) by standardizing to same 1950 world population used by Kurihara et al. (1989). Gao rates are for 1978-82; Geng, 1981-82. For -10 years, Gao and Geng are 1973-75 rates standardized to the 1960 world population from China Map Press (1979). Gao -20 years value is nonadjusted 1961 rate from Kaplan and Tsuchitani (1978).

[4] Where rates for the period were not available in Kurihara et al. (1989), substitutions were made as follows: Kalandidi from 1984-85 rates; Kabat 1982-83; Katada 1982-83; Lam, T. 1984-85; Pershagen 1952-53; Shimizu 1982-83; Sobue 1982-83; Svensson 1982-83.

[5] World-standardized rate for 1961-65 from Katsouyanni et al. (1990). [In Greek: translation provided by Trichopoulos.]

[6] Accrual period value estimated by multiplying LCMR in Shanghai for period 1978-82 (standardized to the 1950 world population) by the ratio of LCMRs in Liaoning and Heilonjiang to Shanghai, for the period 1973-75 (standardized to the 1960 world population). Data are from China Map Press (1979). Value for -10 years is the 1973-75 rate.

[7] The nested core-control study of Hirayama.

* Data not available.

Table D-2. Parameter values used to partition female lung cancer mortality into component sources[1]

		Ever-smokers		Never-smokers	
Case-Control	Lung Cancer Mortality	Prevalence (%)	Relative Risk	Percent Exposed (%)	Relative Risk
AKIB	6.05	21	2.38	70	1.50
BROW	17.29	29	4.30	15	1.50
BUFF	15.29	59	7.06	84	0.81
CHAN	23.59	26	3.48	47	0.74
CORR	26.00	47	12.40	46	1.90
GAO	18.00	18	2.54	74	1.19
GARF(Coh)	9.45	33	3.50	72	1.15
GENG	27.80	41	2.77	44	2.16
HIRA	5.70	16	3.20	77	1.53
HIRA(Coh)	5.70	16	3.20	77	1.37
HUMB	17.70	41	16.30	56	1.98
INOU	6.53	16	1.66	64	2.55
KABA	13.20	42	5.90	60	0.74
KALA	6.58	17	3.32	60	1.92
KOO	22.61	32	2.77	49	1.54
LAMT	23.46	24	3.77	45	1.64
LAMW	22.88	22	4.12	56	2.51
LEE	17.11	60	4.61	68	1.01
SOBU	7.46	21	2.81	54	1.13
SVEN	7.72	43	5.97	66	1.19
TRIC	6.40	11	2.81	52	2.08
WU	18.15	58	4.38	60	1.31
WUWI	11.60	37	2.24	55	0.78

[1] For studies with data on both ever-smokers and never-smokers. Table entries are drawn from Tables 5-4, B-8 and D-1, which contain explanatory footnotes.

Table D-3. Female lung cancer mortality rates by attributable source[1]

		Baseline Sources[2]		Spousal Smoking		Ever-smoking	
Study	Location	No.	%	No.	%	No.	%
AKIB	Japan	3.47	57	0.96	16	1.61	27
BROW	USA	8.22	48	0.44	3	8.63	50
BUFF	USA	3.34	22	0.00	0	11.95	78
CHAN	HK	14.34	61	0.00	0	9.25	39
CORR	USA	2.89	11	0.63	2	22.47	86
GAO	China	12.36	69	1.42	8	4.22	23
GARF (Coh)	USA	4.67	49	0.33	4	4.44	47
GENG	China	10.67	38	3.21	12	13.92	50
HIRA (Coh)	Japan	3.28	58	0.78	14	1.63	29
HUMB	USA	1.57	9	0.51	3	15.62	88
INOU	Japan	2.97	45	2.47	38	1.09	17
KABA	USA	4.32	33	0.00	0	8.88	67
KALA	Greece	3.04	46	1.39	21	2.15	33
KOO	HK	11.41	50	2.05	9	9.14	40
LAMT	HK	10.94	47	2.39	10	10.12	43
LAMW	HK	7.35	32	4.85	21	10.68	47
LEE	Eng./Wales	5.37	31	0.01	0	11.73	69
SOBU	Japan	5.05	68	0.28	4	2.13	29
SVEN	Sweden	2.19	28	0.16	2	5.37	70
TRIC	Greece	3.42	53	1.71	27	1.27	20
WU	USA	5.17	28	0.40	2	12.58	69
WUWI	China	7.95	69	0.00	0	3.65	31

[1] Rates are per 100,000 per year. Data not available for GARF, JANE, PERS, SHIM, BUTL(Coh), and HOLE(Coh).
[2] Nonspousal ETS and non-ETS sources.

2501032291

Table D-4. Lung cancer mortality rates of female ever-smokers (ES) and never-smokers (NS) by exposure status[1]

Study	Location	(1) Unexposed NS[2]	(2) Exposed NS[3]	(3) E.S.	(2) As a Percentage of (3)	(2) - (1) As a Percentage of (3) - (1)
AKIB	Japan	3.47	5.21	11.16	47	23
BROW	USA	8.21	12.32	37.99	32	14
BUFF	USA	3.34	3.34	23.59	14	0
CHAN	HK	14.34	14.34	49.91	29	0
CORR	USA	2.89	5.49	50.70	11	5
GAO	China	12.35	14.70	35.79	41	10
GARF (Coh)	USA	4.67	5.37	18.12	30	5
GENG	China	10.66	23.03	44.62	52	36
HIRA (Coh)	Japan	3.28	4.49	13.49	33	12
HUMB	USA	1.57	3.11	39.66	8	4
INOU	Japan	2.96	7.56	9.80	77	67
KABA	USA	4.32	3.78	25.46	17	0
KALA	Greece	3.04	5.84	15.66	37	22
KOO	HK	11.41	17.57	39.98	44	22
LAMT	HK	10.94	17.94	53.12	34	17
LAMW	HK	7.35	18.45	55.89	33	23
LEE	Eng/Wal	5.36	5.42	24.91	22	0
SOBU	Japan	5.05	5.70	15.18	38	6
SVEN	Sweden	2.18	2.60	14.69	18	3
TRIC	Greece	3.41	7.10	14.99	47	32
WU	USA	5.16	6.77	26.85	25	7
WUWI	China	7.95	7.95	17.81	45	0

[1] Rates are per 100,000 per year. Data not available for GARF, JANE, PERS, SHIM, BUTL(Coh), and HOLE(Coh).
[2] Exposed to baseline sources--nonspousal ETS and non-ETS sources.
[3] Exposed to baseline sources plus spousal ETS.

APPENDIX E. STATISTICAL FORMULAE

E.1. CELL FREQUENCIES

The observed outcome of a case-control study or a cohort study may be depicted in a 2 x 2 table, where a, b, c, and d are cell frequencies.

		ETS Exposed	
		Yes	No
Lung Cancer Present	Yes	a	b
	No	c	d

E.2. CASE-CONTROL STUDIES

The true (but unknown) odds ratio is estimated by the observed odds ratio (OR),

$$OR = ad/bc.$$

A confidence interval on the (true) odds ratio may be calculated from the normal approximation to the distribution of log(OR), the natural logarithm of OR (Woolf, 1955). The variance of log(OR) is estimated by

$$Var(\log(OR)) = 1/a + 1/b + 1/c + 1/d$$

and the standard error by its square root,

$$SE(\log(OR)) = (Var(\log(OR)))^{½}.$$

Approximate 90% confidence limits are given by

$$\log(OR) \pm 1.645\ SE(\log(OR)).$$

The value 1.645 is replaced by 1.96 for 95% confidence limits and, in general, by $Z_{\alpha/2}$ for $100(1 - \alpha)$% confidence limits. The confidence bounds obtained in this way are sometimes called *logit limits* (Breslow and Day, 1980; p.134). Significance level (P-value) of a test for effect, i.e., H_o: (true) odds ratio = 1 against the alternative H_a: (true) odds ratio > 1, is the area under the standard normal curve to the right of the value of the *test statistic*, given by log(OR)/SE(log(RR)).

If the (true) odds ratios are assumed to be equal in k studies, then a pooled estimate is calculated from

$$\log(OR(P)) = \sum w_i \log(OR)_i / \sum w_i$$

where the summations are on i, from 1 to k; OR(P) is the pooled estimate; $\log(OR)_i$ is the logarithm of OR from the i^{th} study; and $w_i = (Var(\log(OR)_i))^{-1}$ is the *weight* of the i^{th} study (Breslow and Day, 1980).

E.3. COHORT STUDIES

The true (but unknown) relative risk is estimated by the observed relative risk (RR),

$$RR = (a/a+c)/(b/b+d).$$

A confidence interval on the (true) relative risk may be calculated from the normal approximation to the distribution of log(RR), using the analogue of Woolf's method referred to above (Katz et al., 1978). The variance of log(RR) is estimated by,

$$Var(\log(RR)) = c/(a^2 + ac) + d/(b^2 + bd)$$

and the standard error by its square root,

$$SE(\log(RR)) = (Var(\log(RR)))^{½}.$$

The remaining calculations follow the description for case-control studies in Section E.2 with "odds ratio" and "OR" replaced by "relative risk" and "RR," respectively. The pooled estimate of relative risk from both case-control and cohort studies is calculated by the same methodology for pooling estimates from case-control studies or from cohort studies separately, i.e., the logarithm of each individual estimate is weighted inversely proportional to its estimated variance (Kleinbaum et al., 1982).

☆ U.S. GOVERNMENT PRINTING OFFICE: 1992 — 650 - 572

United States
Environmental Protection
Agency

Center for Environmental Research
Information
Cincinnati, OH 45268

BULK RATE
POSTAGE & FEES PAII
EPA
PERMIT No. G-35

2501032295

Official Business
Penalty for Private Use, $300

Please make all necessary changes on the above label, detach or copy, and return to the address in the upper left-hand corner.

If you do not wish to receive these reports CHECK HERE ☐ : detach, or copy this cover, and return to the address in the upper left-hand corner.

EPA/600/6-90/006B